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(54) **HUMAN ANTIGEN BINDING PROTEINS THAT BIND β-KLOTHO, FGF RECEPTORS AND COMPLEXES THEREOF**

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(57) **ABSTRACT**

The present invention provides compositions and methods relating to or derived from antigen binding proteins activate FGF21-mediated signaling. In embodiments, the antigen binding proteins specifically bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In some embodiments the antigen binding proteins induce FGF21-like signaling. In some embodiments, an antigen binding protein is a fully human, humanized, or chimeric antibodies, binding fragments and derivatives of such antibodies, and polypeptides that specifically bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Other embodiments provide nucleic acids encoding such antigen binding proteins, and fragments and derivatives thereof, and polypeptides, cells comprising such polynucleotides, methods of making such antigen binding proteins, and fragments and derivatives thereof, and polypeptides, and methods of using such antigen binding proteins, fragments and derivatives thereof, and polypeptides, including methods of treating or diagnosing subjects suffering from type 2 diabetes, obesity, NASH, metabolic syndrome and related disorders or conditions.

3 Claims, 56 Drawing Sheets

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FIG.1A

```
                    1                                                  50
hu FGFR1      (1)   MWSWKCLLFWAVLVTATLCTARPSPTLPEQAQPWGAPVEVESFLVHPGDL
  muFGFR1     (1)   MWGWKCLLFWAVLVTATLCTARPAPTLPEQAQPWGVPVEVESLLVHPGDL
Consensus     (1)   MW WKCLLFWAVLVTATLCTARPAPTLPEQAQPWG PVEVES LVHPGDL
                    51                                                100
hu FGFR1     (51)   LQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADSGLYA
  muFGFR1    (51)   LQLRCRLRDDVQSINWLRDGVQLVESNRTRITGEEVEVRDSIPADSGLYA
Consensus    (51)   LQLRCRLRDDVQSINWLRDGVQL ESNRTRITGEEVEV DSIPADSGLYA
                    101                                               150
hu FGFR1    (101)   CVTSSPSGSDTTYFSVNVSDALPSSEDDDDDDDSSSEEKETDNTKPNRMP
  muFGFR1   (101)   CVTSSPSGSDTTYFSVNVSDALPSSEDDDDDDDSSSEEKETDNTKPNRRP
Consensus   (101)   CVTSSPSGSDTTYFSVNVSDALPSSEDDDDDDDSSSEEKETDNTKPNR P
                    151                                               200
hu FGFR1    (151)   VAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEFKPD
  muFGFR1   (151)   VAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEFKPD
Consensus   (151)   VAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEFKPD
                    201                                               250
hu FGFR1    (201)   HRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEYGSINHTYQLDVVER
  muFGFR1   (201)   HRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEYGSINHTYQLDVVER
Consensus   (201)   HRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEYGSINHTYQLDVVER
                    251                                               300
hu FGFR1    (251)   SPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKI
  muFGFR1   (251)   SPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKI
Consensus   (251)   SPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKI
                    301                                               350
hu FGFR1    (301)   GPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLS
  muFGFR1   (301)   GPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLS
Consensus   (301)   GPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLS
                    351                                               400
hu FGFR1    (351)   HHSAWLTVLEALEERPAVMTSPLYLEIIIYCTGAFLISCMVGSVIVYKMK
  muFGFR1   (351)   HHSAWLTVLEALEERPAVMTSPLYLEIIIYCTGAFLISCMLGSVIIYKMK
Consensus   (351)   HHSAWLTVLEALEERPAVMTSPLYLEIIIYCTGAFLISCMLGSVIIYKMK
                    401                                               450
hu FGFR1    (401)   SGTKKSDFHSQMAVHKLAKSIPLRRQVTVSADSSASMNSGVLLVRPSRLS
  muFGFR1   (401)   SGTKKSDFHSQMAVHKLAKSIPLRRQVTVSADSSASMNSGVLLVRPSRLS
Consensus   (401)   SGTKKSDFHSQMAVHKLAKSIPLRRQVTVSADSSASMNSGVLLVRPSRLS
                    451                                               500
hu FGFR1    (451)   SSGTPMLAGVSEYELPEDPRWELPRDRLVLGKPLGEGCFGQVVLAEAIGL
  muFGFR1   (451)   SSGTPMLAGVSEYELPEDPRWELPRDRLVLGKPLGEGCFGQVVLAEAIGL
Consensus   (451)   SSGTPMLAGVSEYELPEDPRWELPRDRLVLGKPLGEGCFGQVVLAEAIGL
                    501                                               550
hu FGFR1    (501)   DKDKPNRVTKVAVKMLKSDATEKDLSDLISEMEMMKMIGKHKNIINLLGA
  muFGFR1   (501)   DKDKPNRVTKVAVKMLKSDATEKDLSDLISEMEMMKMIGKHKNIINLLGA
Consensus   (501)   DKDKPNRVTKVAVKMLKSDATEKDLSDLISEMEMMKMIGKHKNIINLLGA
                    551                                               600
hu FGFR1    (551)   CTQDGPLYVIVEYASKGNLREYLQARRPPGLEYCYNPSHNPEEQLSSKDL
  muFGFR1   (551)   CTQDGPLYVIVEYASKGNLREYLQARRPPGLEYCYNPSHNPEEQLSSKDL
Consensus   (551)   CTQDGPLYVIVEYASKGNLREYLQARRPPGLEYCYNPSHNPEEQLSSKDL
                    601                                               650
hu FGFR1    (601)   VSCAYQVARGMEYLASKKCIHRDLAARNVLVTEDNVMKIADFGLARDIHH
  muFGFR1   (601)   VSCAYQVARGMEYLASKKCIHRDLAARNVLVTEDNVMKIADFGLARDIHH
Consensus   (601)   VSCAYQVARGMEYLASKKCIHRDLAARNVLVTEDNVMKIADFGLARDIHH
```

FIG.1B

```
                    651                                               700
hu FGFR1     (651)  IDYYKKTTNGRLPVKWMAPEALFDRIYTHQSDVWSFGVLLWEIFTLGGSP
  muFGFR1    (651)  IDYYKKTTNGRLPVKWMAPEALFDRIYTHQSDVWSFGVLLWEIFTLGGSP
Consensus    (651)  IDYYKKTTNGRLPVKWMAPEALFDRIYTHQSDVWSFGVLLWEIFTLGGSP
                    701                                               750
hu FGFR1     (701)  YPGVPVEELFKLLKEGHRMDKPSNCTNELYMMMRDCWHAVPSQRPTFKQL
  muFGFR1    (701)  YPGVPVEELFKLLKEGHRMDKPSNCTNELYMMMRDCWHAVPSQRPTFKQL
Consensus    (701)  YPGVPVEELFKLLKEGHRMDKPSNCTNELYMMMRDCWHAVPSQRPTFKQL
                    751                                               800
hu FGFR1     (751)  VEDLDRIVALTSNQEYLDLSMPLDQYSPSFPDTRSSTCSSGEDSVFSHEP
  muFGFR1    (751)  VEDLDRIVALTSNQEYLDLSIPLDQYSPSFPDTRSSTCSSGEDSVFSHEP
Consensus    (751)  VEDLDRIVALTSNQEYLDLSIPLDQYSPSFPDTRSSTCSSGEDSVFSHEP
                    801                   822
hu FGFR1     (801)  LPEEPCLPRHPAQLANGGLKRR
  muFGFR1    (801)  LPEEPCLPRHPTQLANSGLKRR
Consensus    (801)  LPEEPCLPRHP QLAN GLKRR
```

FIG. 2A

```
                           1                                                  50
hu beta Klotho       (1)   MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
mu beta klotho       (1)   MKTGCAAGSPGNEWIFFSSDERNTRSRKTMSNRALQRSAVLSAFVLLRAV
     Consensus       (1)   MK GCAAGSPGNEWIFFSSDE  TR R TMSN ALQRS ILSA ILLRAV
                           51                                                100
hu beta Klotho      (51)   TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
mu beta klotho      (51)   TGFSGDGKAIWDKKQYVSPVNPSQLFLYDTFPKNFSWGVGTGAFQVEGSW
     Consensus      (51)   TGFSGDGKAIW K     SPVN SQLFLYDTFPKNF WGIGTGA QVEGSW
                           101                                               150
hu beta Klotho     (101)   KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
mu beta klotho     (101)   KTDGRGPSIWDRYVYSHLRGVNGTDRSTDSYIFLEKDLLALDFLGVSFYQ
     Consensus     (101)   K DGKGPSIWD FIHSHLK V  T  SSDSYIFLEKDL ALDFIGVSFYQ
                           151                                               200
hu beta Klotho     (151)   FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL
mu beta klotho     (151)   FSISWPRLFPNGTVAAVNAQGLRYYRALLDSLVLRNIEPIVTLYHWDLPL
     Consensus     (151)   FSISWPRLFP G V   NA GL YY  LLDALVLRNIEPIVTLYHWDLPL
                           201                                               250
hu beta Klotho     (201)   ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
mu beta klotho     (201)   TLQEEYGGWKNATMIDLFNDYATYCFQTFGDRVKYWITIHNPYLVAWHGF
     Consensus     (201)    LQE YGGWKN TIIDIFNDYATYCFQ FGDRVKYWITIHNPYLVAWHGF
                           251                                               300
hu beta Klotho     (251)   GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
mu beta klotho     (251)   GTGMHAPGEKGNLTAVYTVGHNLIKAHSKVWHNYDKNFRPHQKGWLSITL
     Consensus     (251)   GTGMHAPGEKGNL AVYTVGHNLIKAHSKVWHNY   FRPHQKGWLSITL
                           301                                               350
hu beta Klotho     (301)   GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
mu beta klotho     (301)   GSHWIEPNRTDNMEDVINCQHSMSSVLGWFANPIHGDGDYPEFMKTG--A
     Consensus     (301)   GSHWIEPNRSDN  DI  CQ SM SVLGWFANPIHGDGDYPE MK    A
```

FIG. 2B

```
                         351                                               400
hu beta Klotho     (351) VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
mu beta klotho     (349) MIPEFSEAEKEEVRGTADFFAFSFGPNNFRPSNTVVKMGQNVSLNLRQVL
     Consensus     (351) MIP FSEAEK EMRGTADFFAFSFGPNNFKP NTM KMGQNVSLNLR  L
                         401                                               450
hu beta Klotho     (401) NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
mu beta klotho     (399) NWIKLEYDDPQILISENGWFTDSYIKTEDTTAIYMMKNFLNQVLQAIKFD
     Consensus     (401) NWIKLEY  P ILIAENGWFTDS IKTEDTTAIYMMKNFL QVLQAIK D
                         451                                               500
hu beta Klotho     (451) EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
mu beta klotho     (449) EIRVFGYTAWTLLDGFEWQDAYTTRRGLFYVDFNSEQKERKPKSSAHYYK
     Consensus     (451) EIRVFGYTAWSLLDGFEWQDAYT RRGLFYVDFNS QKERKPKSSAHYYK
                         501                                               550
hu beta Klotho     (501) QIIRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHL
mu beta klotho     (499) QIIQDNGFPLKESTPDMKGRFPCDFSWGVTESVLKPEFTVSSPQFTDPHL
     Consensus     (501) QII DNGF LKESTPDM G FPCDFSWGVTESVLKPE   SSPQFSDPHL
                         551                                               600
hu beta Klotho     (551) YVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA
mu beta klotho     (549) YVWNVTGNRLLYRVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFA
     Consensus     (551) YVWN TGNRLLHRVEGVRLKTRPAQCTDFV IKK LEMLAKMKVTHY FA
                         601                                               650
hu beta Klotho     (601) LDWASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLG
mu beta klotho     (599) LDWTSILPTGNLSKVNRQVLRYYRCVVSEGLKLGVFPMVTLYHPTHSHLG
     Consensus     (601) LDW SILPTGNLS VNRQ LRYYRCVVSEGLKLGI  MVTLYHPTHAHLG
                         651                                               700
hu beta Klotho     (651) LPEPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDI
mu beta klotho     (649) LPLPLLSSGGWLNMNTAKAFQDYAELCFRELGDLVKLWITINEPNRLSDM
     Consensus     (651) LP PLL A GWLN  TA AFQ YA LCF ELGDLVKLWITINEPNRLSDI
```

FIG. 2C

```
                          701                                               750
hu beta Klotho     (701)  YNRSGNDTYGAAHNLLVAHALAWRLYDRQFRPSQRGAVSLSLHADWAEPA
mu beta klotho     (699)  YNRTSNDTYRAAHNLMIAHAQVWHLYDRQYRPVQHGAVSLSLHCDWAEPA
     Consensus     (701)  YNRS NDTY AAHNLLIAHA  W LYDRQFRP Q GAVSLSLH DWAEPA
                          751                                               800
hu beta Klotho     (751)  NPYADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSS
mu beta klotho     (749)  NPFVDSHWKAAERFLQFEIAWFADPLFKTGDYPSVMKEYIASKNQRGLSS
     Consensus     (751)  NPF DSHWKAAERFLQFEIAWFADPLFKTGDYPA MKEYIASK  RGLSS
                          801                                               850
hu beta Klotho     (801)  SALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFL
mu beta klotho     (799)  SVLPRFTAKESRLVKGTVDFYALNHFTTRFVIHKQLNTNRSVADRDVQFL
     Consensus     (801)  S LPR T  E RLLKGTVDF ALNHFTTRFVIH QL   R  ADRDIQFL
                          851                                               900
hu beta Klotho     (851)  QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD
mu beta klotho     (849)  QDITRLSSPSRLAVTPWGVRKLLAWIRRNYRDRDIYITANGIDDLALEDD
     Consensus     (851)  QDITRLSSPSRLAV PWGVRKLL WIRRNY D DIYITA GIDD ALEDD
                          901                                               950
hu beta Klotho     (901)  RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK
mu beta klotho     (899)  QIRKYYLEKYVQEALKAYLIDKVKIKGYYAFKLTEEKSKPRFGFFTSDFR
     Consensus     (901)   IRKYYL KYLQE LKAYLIDKVKIKGYYAFKL EEKSKPRFGFFTSDFK
                          951                                              1000
hu beta Klotho     (951)  AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
mu beta klotho     (949)  AKSSVQFYSKLISSSGLPAENRSPACGQPAEDTDCTICSFLVEKKPLIFF
     Consensus     (951)  AKSSIQFY KLISS G P EN S  C Q  E TDCTIC FLV KKPLIF
                          1001                                         1045
hu beta Klotho    (1001)  GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS-
mu beta klotho     (999)  GCCFISTLAVLLSITVFHHQKRRKFQKARNLQNIPLKKGHSRVFS
     Consensus    (1001)  GCCF STL LLLSI IF  QKRRKF KAKNLQ IPLKKG   V
```

FIG. 3A

AM-1 Parental-Unstained

DB120707-AM1 Unstained

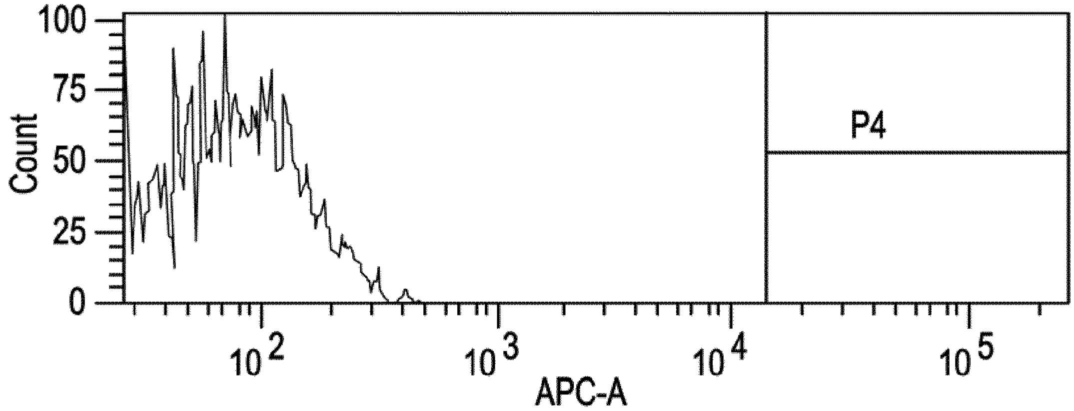


FIG. 3B

AM-1 /bKlotho +FGFR1 pool 3 - Unstained

DB120707-Pool3 Unstained

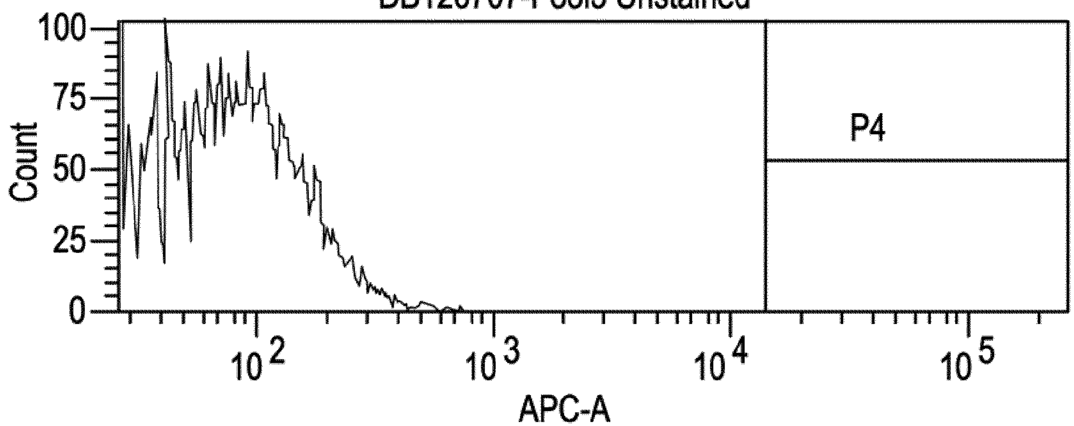


FIG. 3C

CHO/bKlotho+FGFR1 pool 5- Unstained

DB120707-Pool5 Unstained

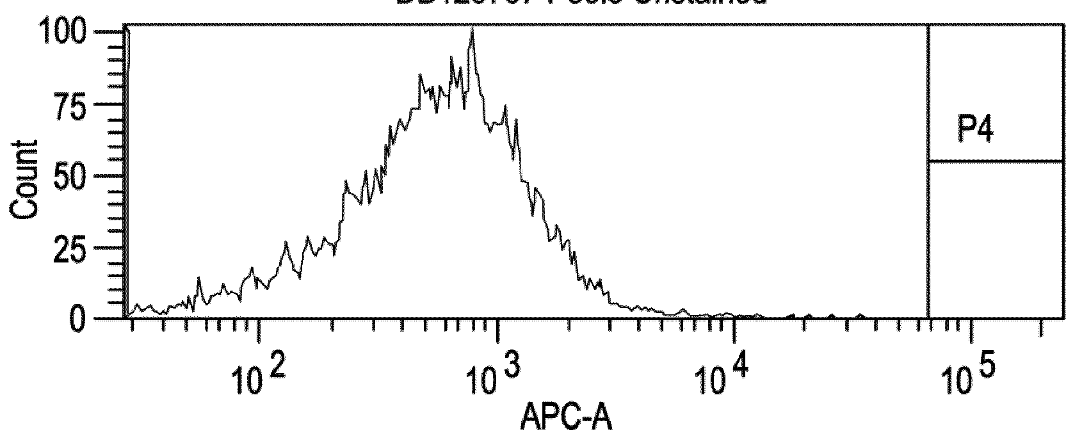


FIG. 3D

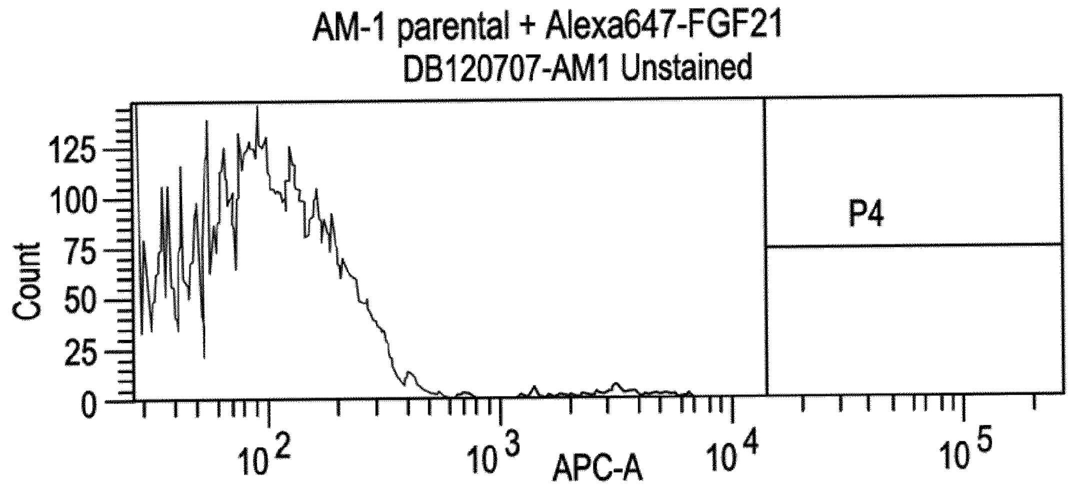


FIG. 3E

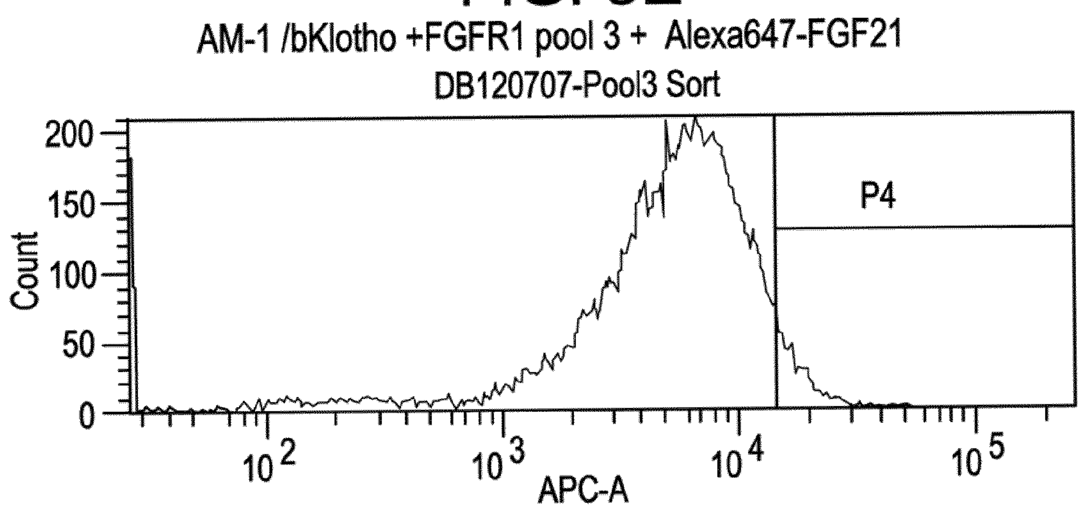


FIG. 3F

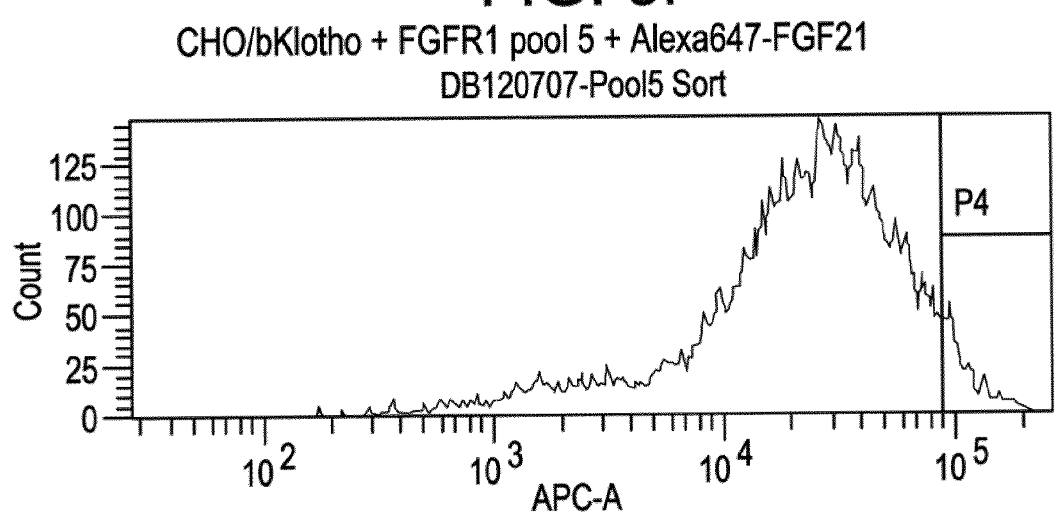


FIG. 4

DPSPTLPEQAQPWGAPVEVESFLVHPGDLLQLRCRLRDDVQSINWLRDGVQL
AESNRTRITGEEVEVQDSVPADSGLYACVTSSPSGSDTTYFSVNVSDALPSS
EDDDDDDDSSSEEKETDNTKPNRMPVAPYWTSPEKMEKKLHAVPAAKTVKFK
CPSSGTPNPTLRWLKNGKEFKPDHRIGGYKVRYATWSIIMDSVVPSDKGNYT
CIVENEYGSINHTYQLDVVERSPHRPILQAGLPANKTVALGSNVEFMCKVYS
DPQPHIQWLKHIEVNGSKIGPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSF
EDAGEYTCLAGNSIGLSHHSAWLTVLEALEERPAVMTSPLY*ggggg*dkthtc
ppcpapellggpsvflfppkpkdtlmisrtpevtcVvvdvshedpevkfnwy
vdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkeyKckvsnkalpa
piektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewE
sngqpennykttppvldsdgsfflyskltvdksrwqqgnvfscsvmhealhn
hytqkslslspgk

FIG. 5

```
FSGDGRAI WSKNPNFTPV NESQLFLYDT FPKNFFWGIG TGALQVEGSW
KKDGKGPSIW DHFIHTHLKN VSSTNGSSDS YIFLEKDLSA LDFIGVSFYQ
FSISWPRLFP DGIVTVANAK GLQYYSTLLD ALVLRNIEPI VTLYHWDLPL
ALQEKYGGWK NDTIIDIFND YATYCFQMFG DRVKYWITIH NPYLVAWHGY
GTGMHAPGEK GNLAAVYTVG HNLIKAHSKV WHNYNTHFRP HQKGWLSITL
GSHWIEPNRS ENTMDIFKCQ QSMVSVLGWF ANPIHGDGDY PEGMRKKLFS
VLPIFSEAEK HEMRGTADFF AFSFGPNNFK PLNTMAKMGQ NVSLNLREAL
NWIKLEYNNP RILIAENGWF TDSRVKTEDT TAIYMMKNFL SQVLQAIRLD
EIRVFGYTAW SLLDGFEWQD AYTIRRGLFY VDFNSKQKER KPKSSAHYYK
QIIRENGFSL KESTPDVQGQ FPCDFSWGVT ESVLKPESVA SSPQFSDPHL
YVWNATGNRL LHRVEGVRLK TRPAQCTDFV NIKKQLEMLA RMKVTHYRFA
LDWASVLPTG NLSAVNRQAL RYYRCVVSEG LKLGISAMVT LYYPTHAHLG
LPEPLLHADG WLNPSTAEAF QAYAGLCFQE LGDLVKLWIT INEPNRLSDI
YNRSGNDTYG AAHNLLVAHA LAWRLYDRQF RPSQRGAVSL SLHADWAEPA
NPYADSHWRA AERFLQFEIA WFAEPLFKTG DYPAAMREYI ASKHRRGLSS
SALPRLTEAE RRLLKGTVDF CALNHFTTRF VMHEQLAGSR YDSDRDIQFL
QDITRLSSPT RLAVIPWGVR KLLRWVRRNY GDMDIYITAS GIDDQALEDD
RLRKYYLGKY LQEVLKAYLI DKVRIKGYYA FKLAEEKSKP RFGFFTSDFK
AKSSIQFYNK VISSRGFPFE NSSSRCSQTQ ENTECTVCLF LVQKKP
gggggdkthtcppcpapellggpsvflfppkpkdtlmisrtpevtcvvvdvshe
dpevkfnwyvdgvevhnaktkpreeqynstYrvvsvltvlhqdwlngkeykckv
snkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdi
avewesngqpennykttppvldsdgsfflyskltvdksrwqqgnvfscsvmhea
lhnhytqkslslspgk
```

FIG. 6

1. Mol. wt. markers
2. Heterodimer, non-reducing
3. Stds
4. Heterodimer, reducing
5. Mol. wt. markers

FIG. 7A

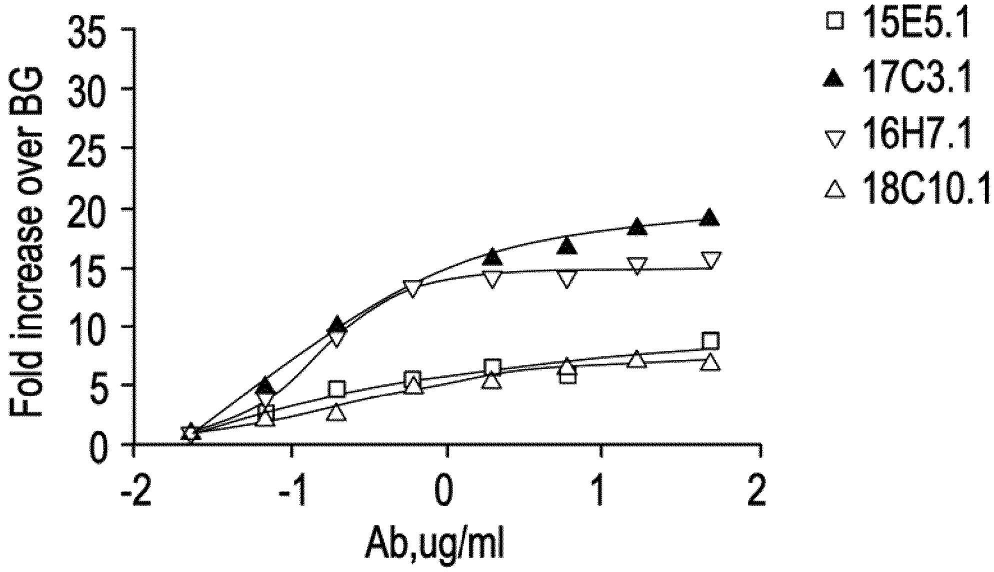

15E5.1
17C3.1
16H7.1
18C10.1
Fold increase over BG
Ab,ug/ml
35
30
25
20
15
10
5
0
-2
-1
0
1
2

FIG. 7B

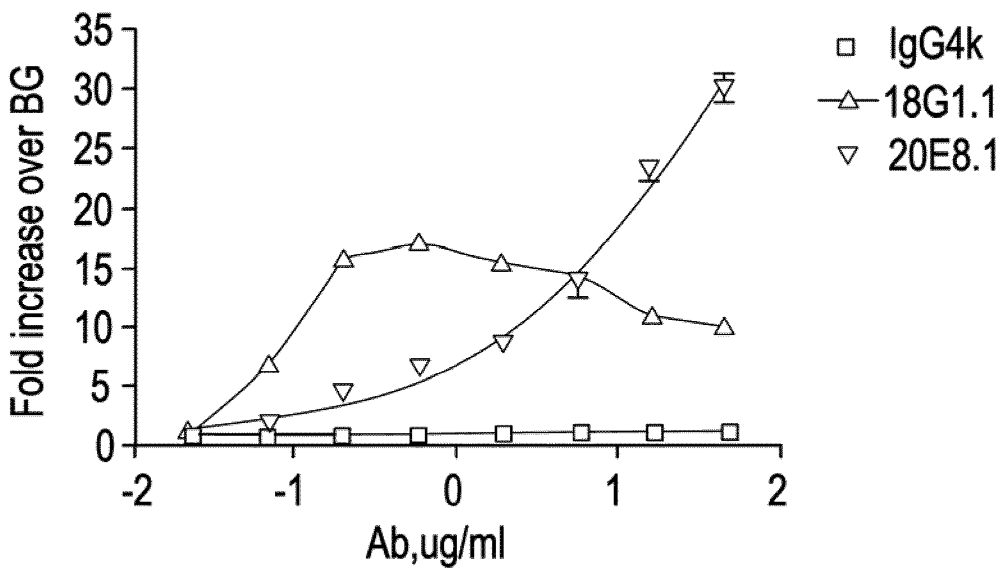

IgG4k
18G1.1
20E8.1
Fold increase over BG
Ab,ug/ml
35
30
25
20
15
10
5
0
-2
-1
0
1
2

FIG. 7C

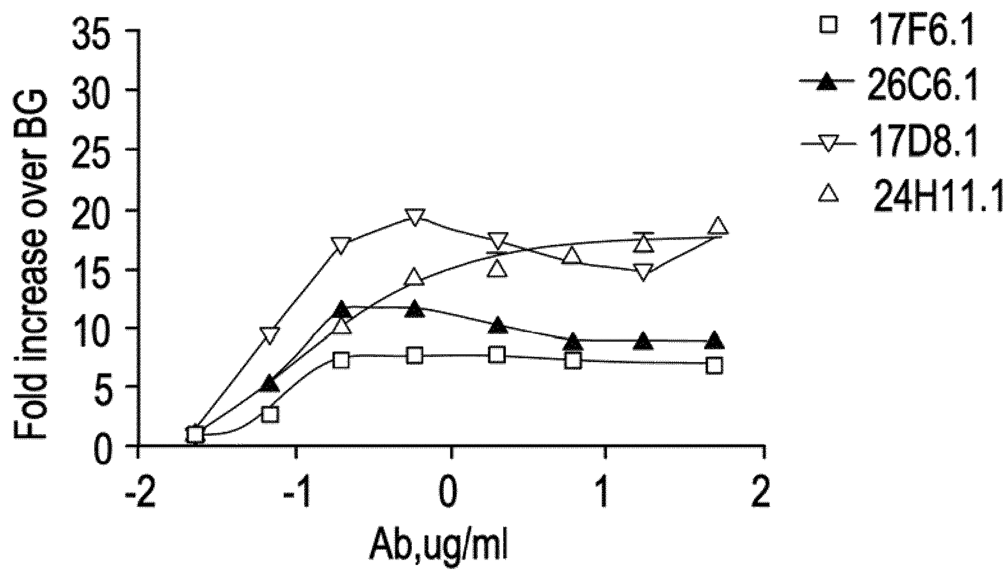

35
30
25
20
15
10
5
0
-2
-1
0
1
2
Fold increase over BG
Ab,ug/ml
17F6.1
26C6.1
17D8.1
24H11.1

FIG. 7D

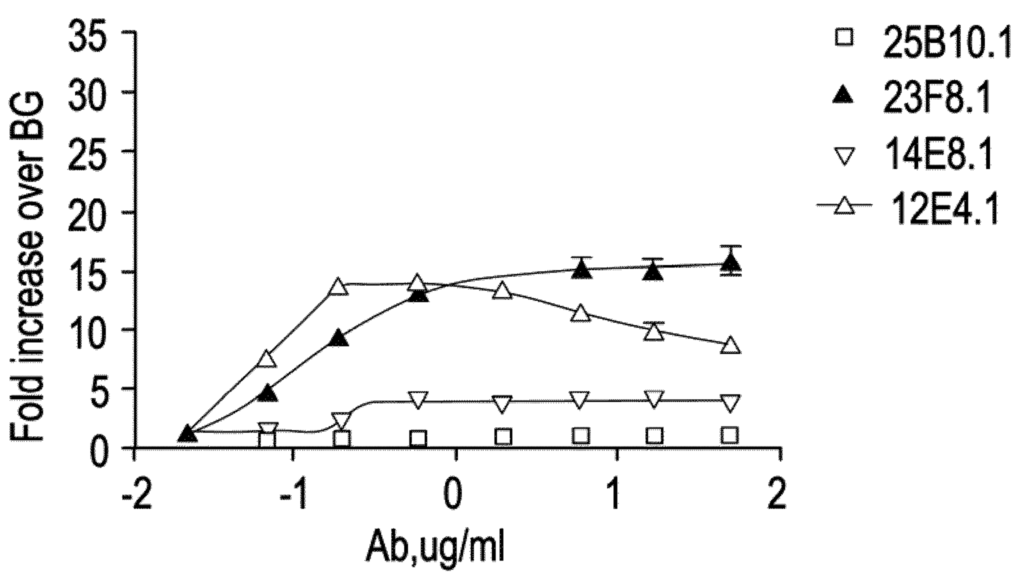

35
30
25
20
15
10
5
0
-2
-1
0
1
2
Fold increase over BG
Ab,ug/ml
25B10.1
23F8.1
14E8.1
12E4.1

FIG. 8A

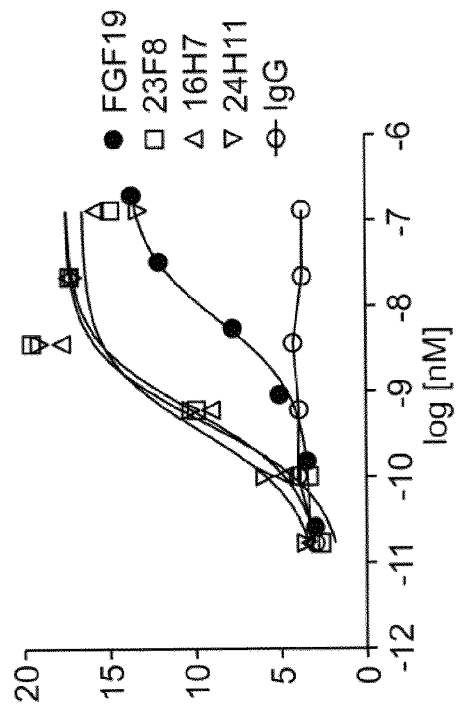


FIG. 8B

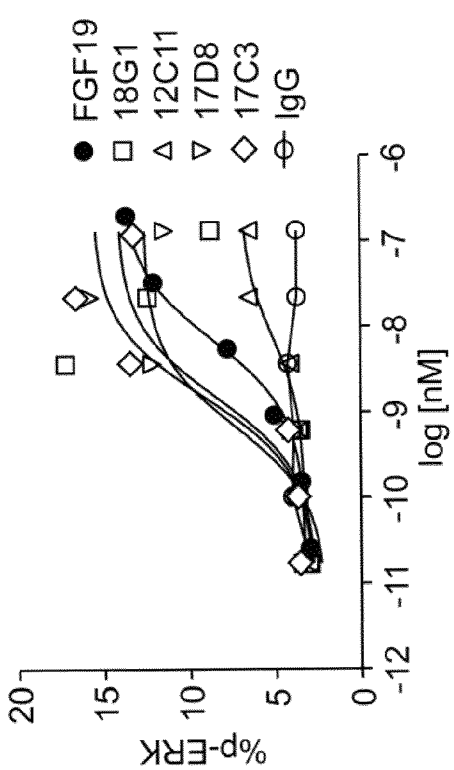


FIG. 8C

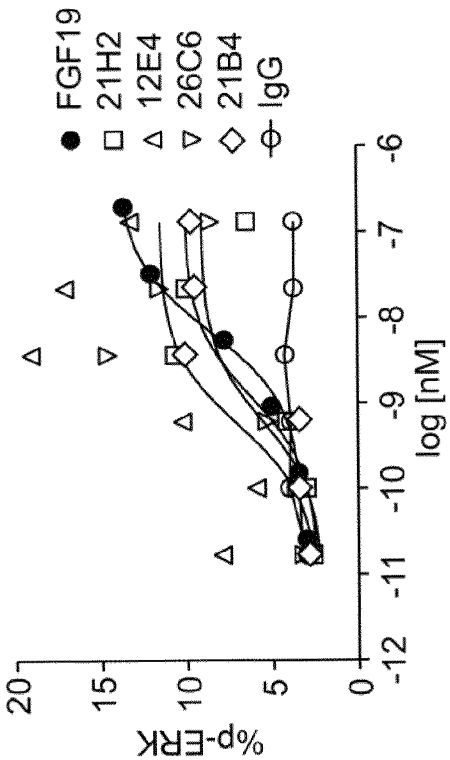


FIG. 9A

FGFR1c + βKlotho

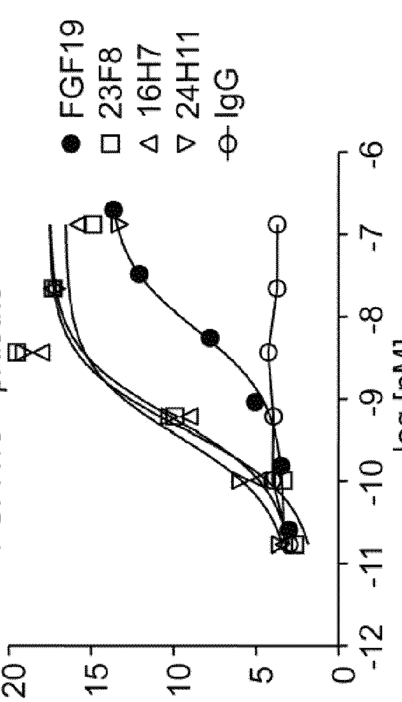


FIG. 9B

FGFR2c + βKlotho

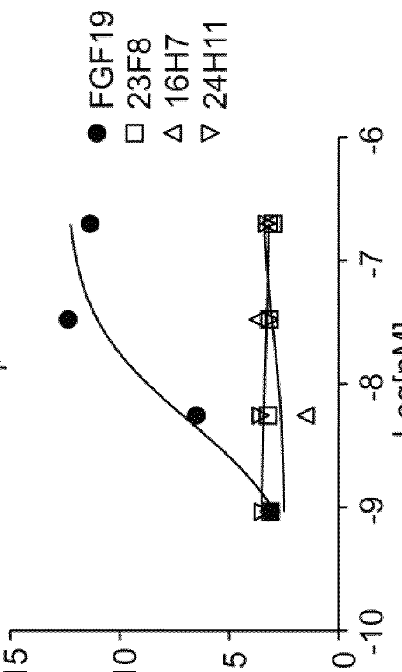


FIG. 9C

FGFR3c + βKlotho

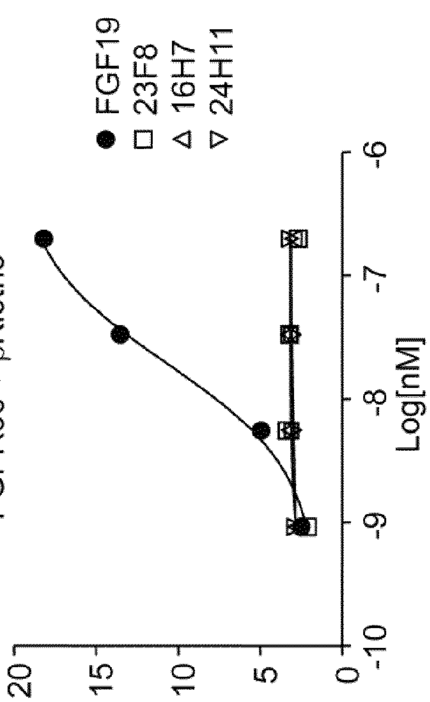


FIG. 9D

FGFR4c + βKlotho

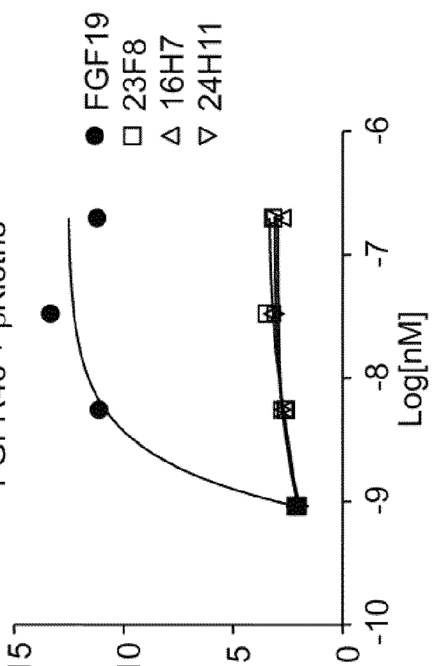


FIG. 10A

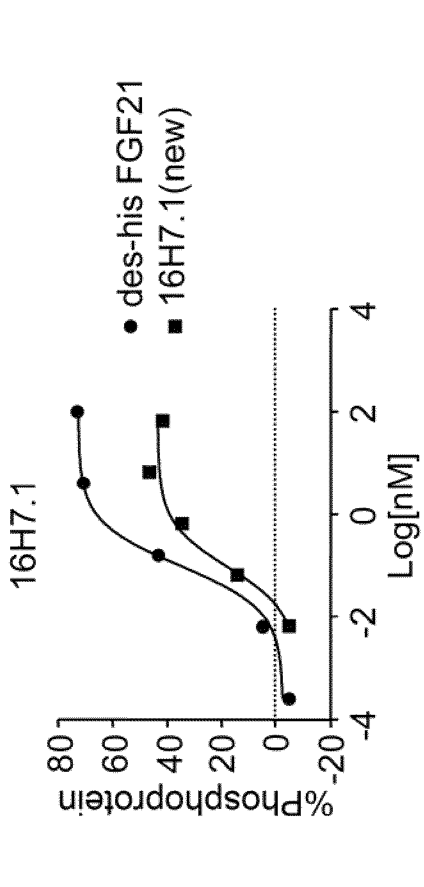


FIG. 10B

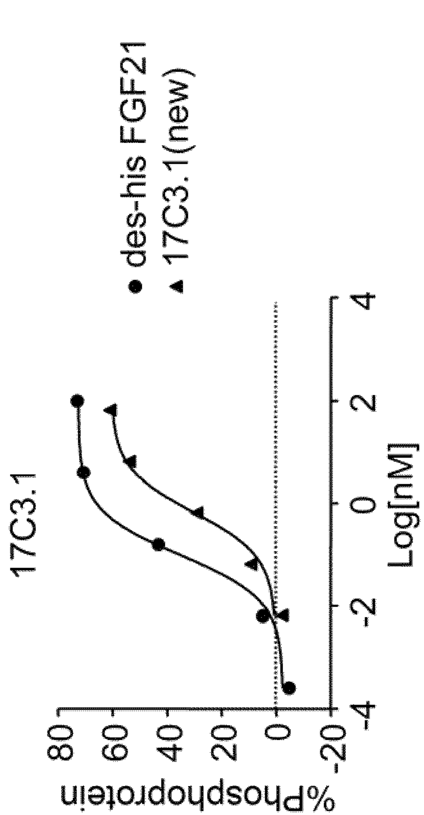


FIG. 10C

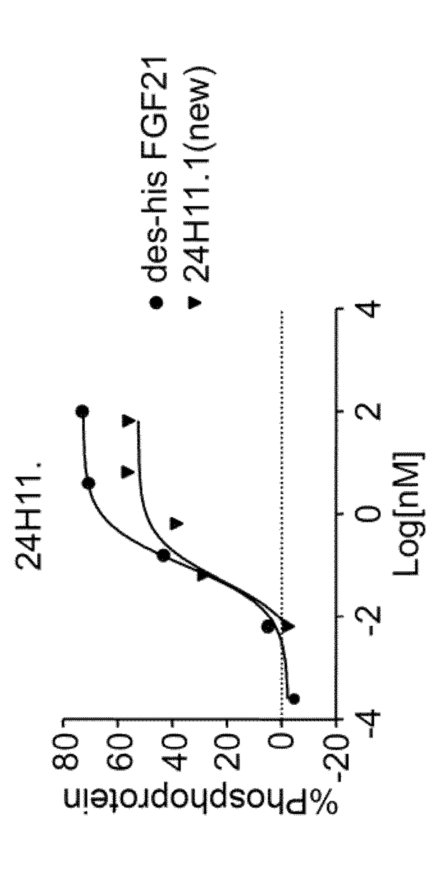


FIG. 10D

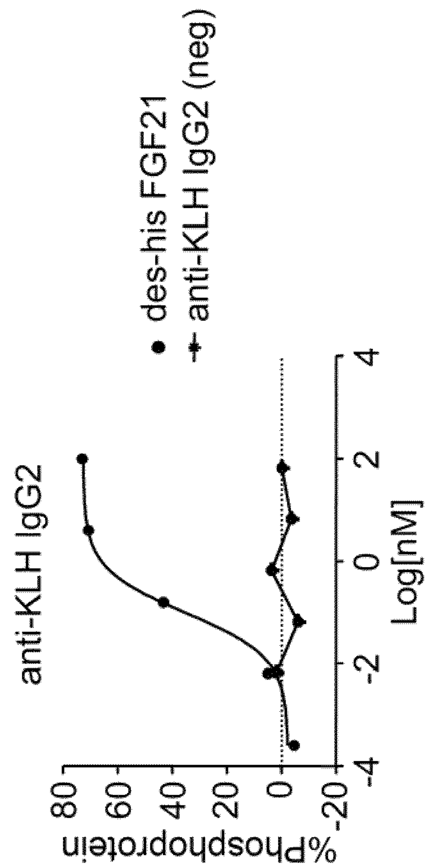
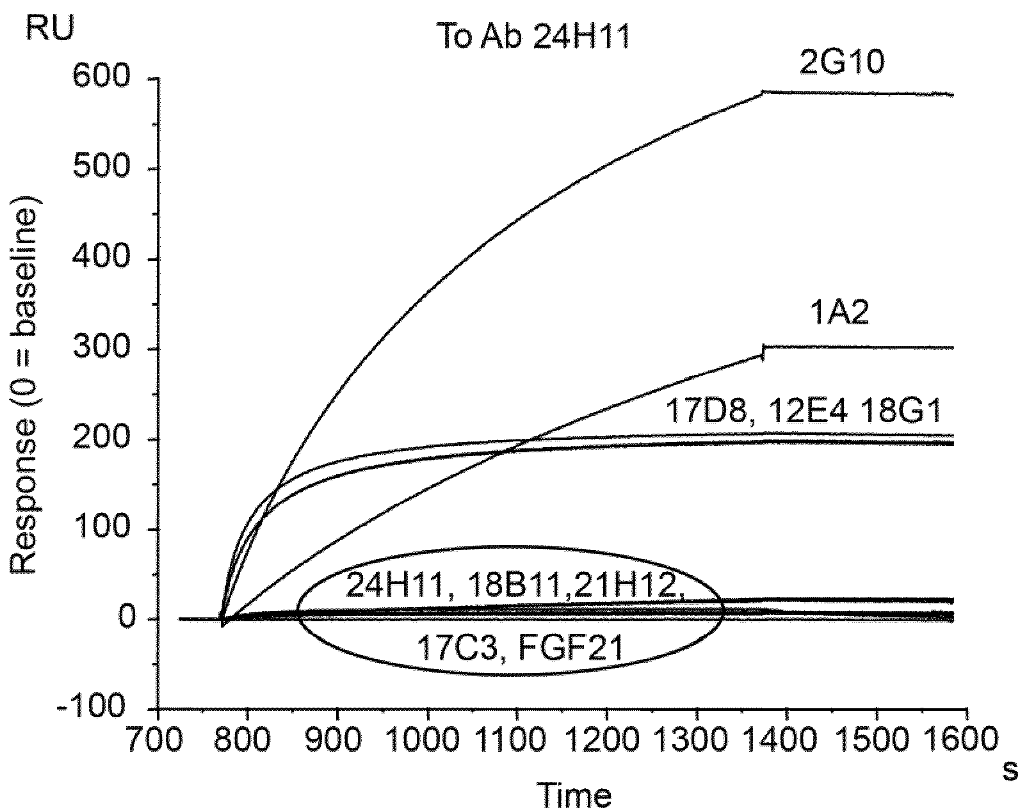
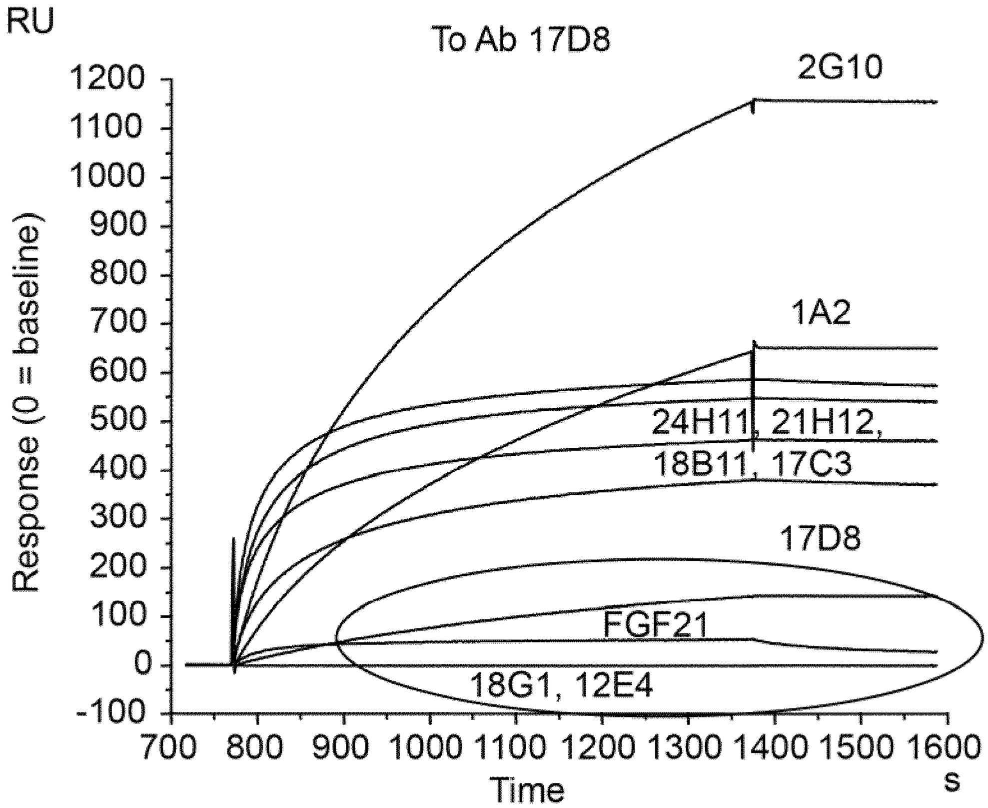


FIG. 11A



RU
To Ab 24H11
2G10
1A2
17D8, 12E4 18G1
24H11, 18B11,21H12,
17C3, FGF21
600
500
400
300
200
100
0
-100
Response (0 = baseline)
700
800
900
1000
1100
1200
1300
1400
1500
1600
s
Time

FIG. 11B



RU
To Ab 17D8
2G10
1A2
24H11, 21H12,
18B11, 17C3
17D8
FGF21
18G1, 12E4
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
Response (0 = baseline)
700
800
900
1000
1100
1200
1300
1400
1500
1600
Time
s

FIG. 11C

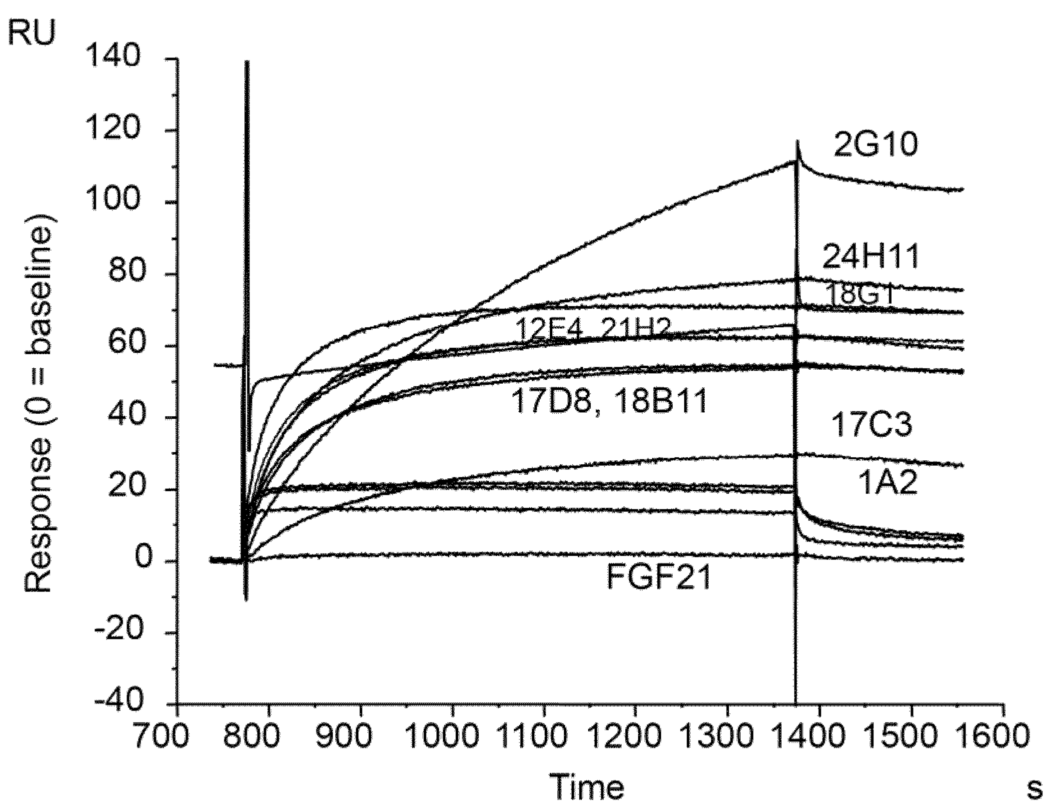

RU
140
120
100
80
60
40
20
0
-20
-40
Response (0 = baseline)
700
800
900
1000
1100
1200
1300
1400
1500
1600
Time
s
2G10
24H11
18G1
12F4, 21H2
17D8, 18B11
17C3
1A2
FGF21

FIG. 11D

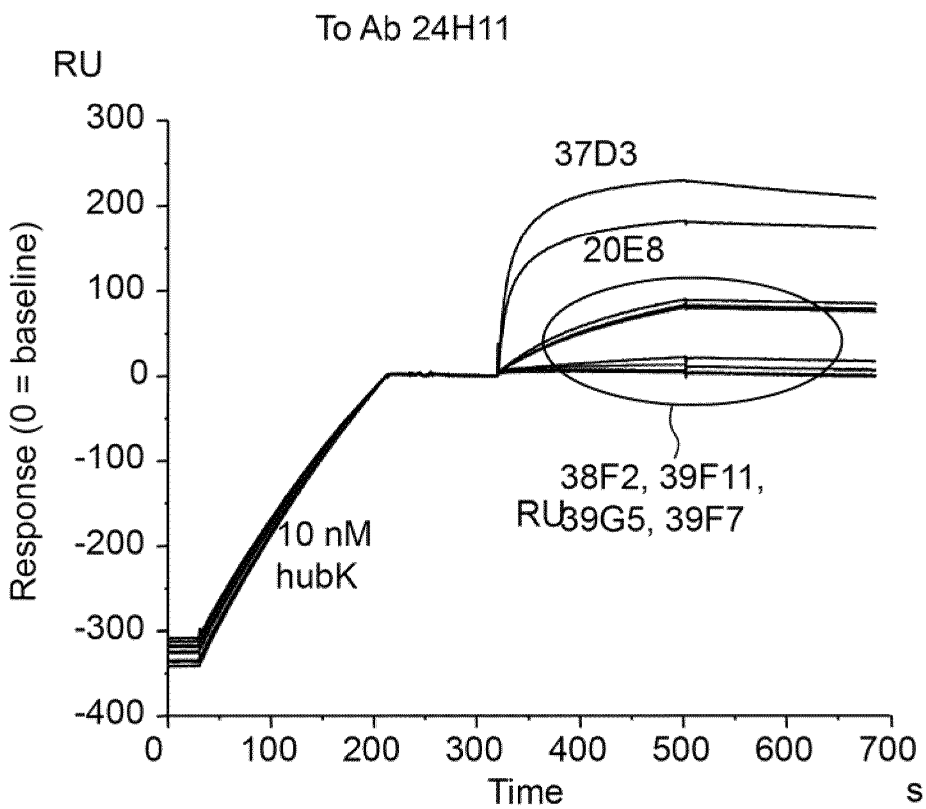

To Ab 24H11
RU
300
200
100
0
-100
-200
-300
-400
Response (0 = baseline)
0
100
200
300
400
500
600
700
Time
s
37D3
20E8
38F2, 39F11,
39G5, 39F7
RU
10 nM
hubK

FIG. 11E

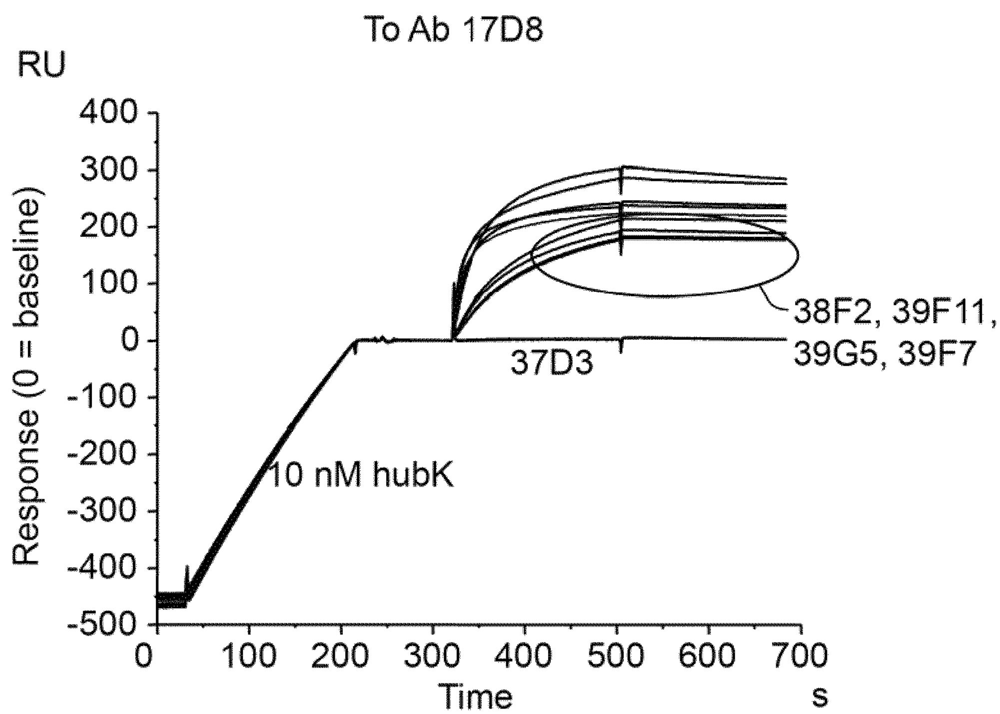

To Ab 17D8
RU
Response (0 = baseline)
400
300
200
100
0
-100
-200
-300
-400
-500
0
100
200
300
400
500
600
700
Time
s
10 nM hubK
37D3
38F2, 39F11,
39G5, 39F7

FIG. 11F

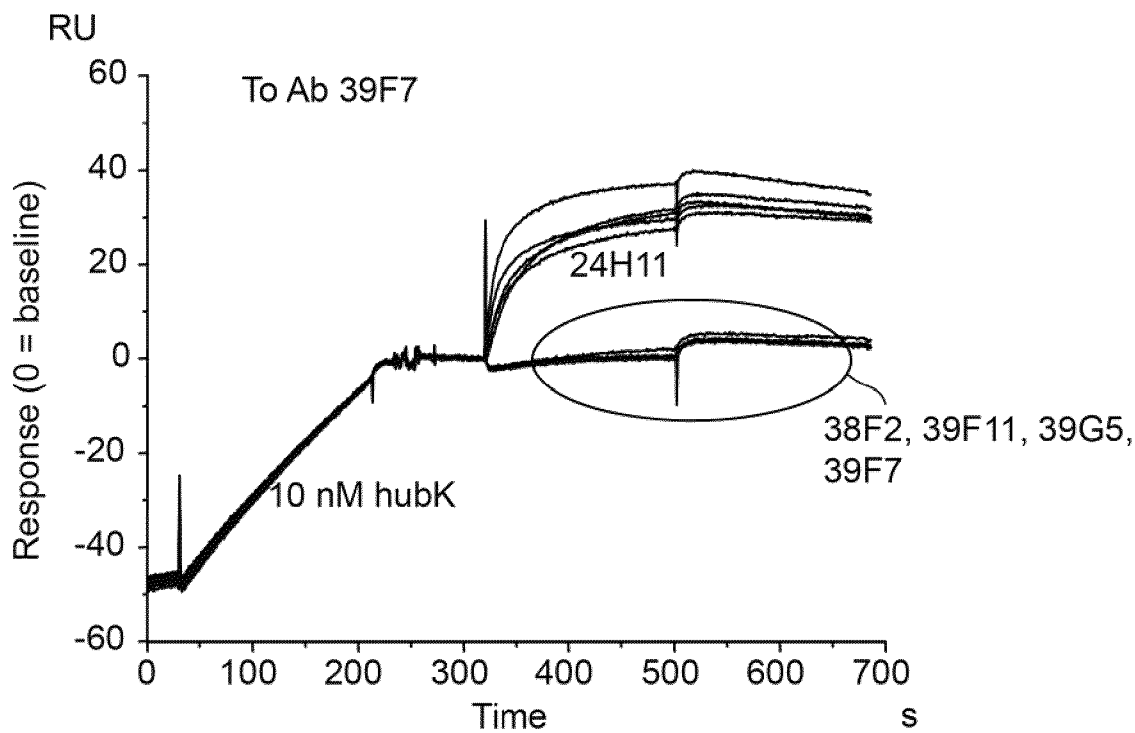

RU
Response (0 = baseline)
To Ab 39F7
24H11
38F2, 39F11, 39G5, 39F7
10 nM hubK
60
40
20
0
-20
-40
-60
0
100
200
300
400
500
600
700
Time
s

FIG. 11G

Epitope Binning Summary

24H11 Bin: 2nd Campaign – 24H11, 17C3, 16H7, 20D4, 21B4, 22H5, 23F8, 21H2, 18B11;
3rd Campaign – 40D2, 46D11

17D8 Bin: 2nd Campaign – 17D8, 12C11, 26H11, 12E4, 18G1;
3rd Campaign – 37D3

39F7 Bin: 3rd Campaign – 39F7, 38F2, 39F11, 39G5

20E8 Bin: 2nd Campaign – 20E8

FIG. 12

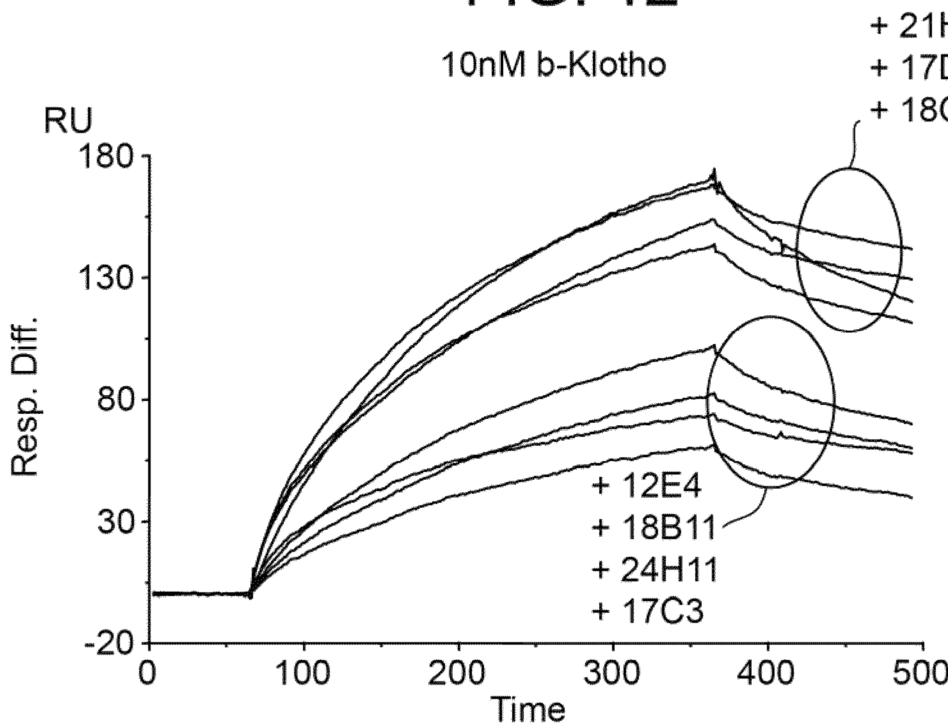

10nM b-Klotho
+ 21H2
+ 17D8
+ 18G1
RU
180
130
80
30
-20
Resp. Diff.
+ 12E4
+ 18B11
+ 24H11
+ 17C3
0
100
200
300
400
500
Time

FIG. 13A

Light chain

	Germline	Germline	FR1
			DIQMTQSPSSLSASVGDRVTITC
20D4	VK1|A30	JK4	---L----------I--------
	Germline	Germline	FR1
			DIQMTQSPSSVSASVGDRVTITC
46D11	VK1|L5	JK5	-----------------------
	Germline	Germline	FR1
			DIVMTQTPLSLSVTPGQPASISC
40D2=36F2=39C2	VK2|A18	JK1	-F---------------------
	Germline	Germline	FR1
			DIVMTQSPLSLPVTPGEPASISC
37D3	VK2|A19	JK2	-----------------------
	Germline	Germline	FR1
			DIVMTQSPLSLPVTPGEPASISC
18B11 LC#1	VK2|A19	JK3	-----------------------
	Germline	Germline	FR1
			EIVLTQSPGTLSLSPGERATLSC
12C11	VK3|A27	JK4	-----------------------
18G1	VK3|A27	JK4	-----------------------
17D8	VK3|A27	JK4	-----------------------
21B4	VK3|A27	JK4	-----------------------
21H2	VK3|A27	JK4	-----------------------
26H11	VK3|A27	JK4	-----------------------
12E4	VK3|A27	JK4	-----------------------
39F7=47E3=38F2	VK3|A27	JK4	-----------------------
39F11=41H5=37G3=39G8	VK3|A27	JK4	-----------------------
39G5	VK3|A27	JK4	-----------------------
	Germline	Germline	FR1
			EIVMTQSPATLSVSPGERATLSC
18B11 LC#2	VK3|L2	JK1	-----------------------
	Germline	Germline	FR1
			SYVLTQPPSVSVAPGKTARITC
16H7=23F8	VL3|3h	JL3	---------------Q------
24H11	VL3|3h	JL3	---------------Q------
22H5	VL3|3h	JL3	---------------Q------
17C3	VL3|3h	JL3	---------------Q------

FIG. 13B

Heavy chain			
	Germline	Germline	FR1
			QVQLVQSGAEVKKPGASVKVSCKVSGYTLT
20D4	VH1|124	JH6	------------------------------
	Germline	Germline	FR1
			QVTLKESGPVLVKPTETLTLTCTVSGFSLS
17C3	VH2|226	JH6	------------------------------
22H5	VH2|226	JH6	------------------------------
16H7=23F8	VH2|226	JH6	-----------------------------N
24H11	VH2|226	JH6	------------------------------
46D11	VH2|226	JH6	------A-----------------------
	Germline	Germline	FR1
			EVQLVESGGGLVKPGGSLRLSCAASGFTFS
18B11	VH3|315	JH6	------------------------------
37D3	VH3|315	JH6	--H--------A-----------------R
	Germline	Germline	FR1
			EVQLLESGGGLVQPGGSLRLSCAASGFTFS
18G1	VH3|323	JH4	-------------------------R----
12C11	VH3|323	JH4	-------------------------R----
12E4	VH3|323	JH4	-------------------------R----
17D8	VH3|323	JH4	----------------Y-------------
26H11	VH3|323	JH4	----------------Y-------------
	Germline	Germline	FR1
			QVQLVESGGGVVQPGRSLRLSCAASGFTFS
39F11=41H5=37G3=39G8	VH3|333	JH6	------------------------------
39F7=47E3=38F2	VH3|333	JH6	------------------------------
39G5	VH3|333	JH6	-----------------------V------
	Germline	Germline	FR1
			QVQLQESGPGLVKPSQTLSLTCTVSGGSIS
40D2=36F2=39C2	VH4|431	JH5	------------------------------

	Germline	Germline	FR1
			QVQLQESGPGLVKPSETLSLTCTVSGGSIS
21B4	VH4|459	JH6	------------------------------
21H2	VH4|459	JH6	------------------------------

FIG. 13C

CDR1	FR2	CDR2
RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS
----D--Y---	---------------	-------
CDR1	**FR2**	**CDR2**
RASQGISSWLA	WYQQKPGKAPKLLIY	AASSLQS
-------I---	---------------	-------
CDR1	**FR2**	**CDR2**
KSSQSLLHSDGKTYLY	WYLQKPGQSPQLLIY	EVSSRFS
-------Q--------	--------P-H----	---N---
CDR1	**FR2**	**CDR2**
RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS
-------------F--	---------------	---D---
CDR1	**FR2**	**CDR2**
RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS
-------YY--FT---	-F--------H----	-------
CDR1	**FR2**	**CDR2**
RASQSVSSSYLA	WYQQKPGQAPRLLIY	GASSRAT
----NFD--S--	---------------	-------
----NFD-----	---------------	-T-----
-------GN---	---------------	-------
--------T---	-H------GL-----	-------
--------T---	-H------GL-----	-------
-------GN---	---------------	-------
----NFD-N---	---------------	-------
--------T---	---------------	-------
--------T---	----------S----	-------
--------T---	---------------	---F---
CDR1	**FR2**	**CDR2**
RASQSVSSNLA	WYQQKPGQAPRLLIY	GASTRAT
------N----	---------------	-V-----
CDR1	**FR2**	**CDR2**
GGNNIGSKSVH	WYQQKPGQAPVLVIY	YDSDRPS
-------E---	-------------V-	D------
-------E---	-------------V-	D------
-------Q---	-------------V-	D------
-------Q---	-------------V-	D------

FIG. 13D

CDR1	FR2	CDR2
ELSMH	WVRQAPGKGLEWMG	GFDPEDGETIYAQKFQG
D----	--------------	-----------------
CDR1	**FR2**	**CDR2**
NARMGVS	WIRQPPGKALEWLA	HIFSNDEKSYSTSLKS
-------	--------------	----------------
-------	--------------	----------------
-------	--------------	----------------
-------	--------------	---------------N
------N	--------------	----------------
CDR1	**FR2**	**CDR2**
NAWMS	WVRQAPGKGLEWVG	RIKSKTDGGTTDYAAPVKG
D----	--------------	-------------------
-----	--------------	-------------------
CDR1	**FR2**	**CDR2**
SYAMS	WVRQAPGKGLEWVS	AISGSGGSTYYADSVKG
T----	--------------	G-----V--H-------
T----	--------------	G-----V----------
T----	--------------	G-----V----------
T----	--------------	------V----------
T----	--------------	------V--N-------
CDR1	**FR2**	**CDR2**
SYGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG
---I-	--------------	-------D---------
N--I-	--------------	-------I---------
---I-	--------------	-------D---G-----
CDR1	**FR2**	**CDR2**
SGGYYWS	WIRQHPGKGLEWIG	YIYYSGSTYYNPSLKS
----N--	--------------	N---------------

CDR1	FR2	CDR2
SYYWS	WIRQPPGKGLEWIG	YIYYSGSTNYNPSLKS
--F--	-----A--------	R--T------------
-----	-----A--------	R--T------------

FIG. 13E

FR3	**CDR3**	**FR4**
GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC		
-----------------V-------------	LQHNSYPLT	FGGGTKVEIE
FR3	**CDR3**	**FR4**
GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC		
--------------------------------	QQANDFPIT	FGQGTRLEIK
FR3	**CDR3**	**FR4**
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC		
--------------------------------	MQSIQLPRT	FGQGTKVEIK
FR3	**CDR3**	**FR4**
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC		
------------E-------------L---	MQALQTPCS	FGQGTKLEIK
FR3	**CDR3**	**FR4**
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC		
---------V----------------------	MQSLQTPFT	FGPGTKVDIK
FR3	**CDR3**	**FR4**
GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC		
---------------------------M---	QQCGSSPLT	FGGGTKVEIK
--------I----------N--------M---	QQYGGSPLT	FGGGTEVEIK
--------------------------------	QQYGSAPLT	FGGGTKVEIK
--------------------------------	QQYGSSFT	FGGGTRVEIK
--------------------------------	QQYGSSFT	FGGGTRVEIK
---------------------------M---	QQYGSSPLT	FGGGSKVEIK
----N----------------------M---	QQYGSSPLT	FGGGTKVEIK
--------------------------------	QQSGSSPLT	FGGGTEVEIK
--------------------------------	QQSGSSPLT	FGGGTKVEIK
--------------------------------	QQSGSSPLT	FGGGTKVEIK
FR3	**CDR3**	**FR4**
GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC		
------------------R------------	QQYNNWPPT	FGQGTKVEIK
FR3	**CDR3**	**FR4**
GIPERFSGSNSGNTATLTISRVEAGDEADYYC		
--------------------------------	QVWDGNSDHVV	FGGGTKLTVL
--------------------------------	QVWDGNSDHVV	FGGGTKLTVL
--------------------------------	QVWDNTSDHVV	FGGGTKLTVL
--------------------------------	QVWDSSSDHVV	FGGGTKLTVL

FIG. 13F

FR3	CDR3	FR4
RVTMTEDTSTDTAYMELSSLRS EDTAVYYCAT		
-I----------------------------S	IVVVPAAIQSYYYYYGMGV	WGQGTTVTVSS

FR3	CDR3	FR4
RLTISKDTSKSQVVLTMTNMDPV DTATYYCAR		
--------------------------------	ILLLGAYYYYGMDV	WGQGTTVTVSS
--------------------------------	ILLVGAYYYCGMDV	WGQGTTVTVSS
---------------I----------------	SVVTGGYYYDGMDV	WGQGTTVTVSS
---------------I----------------	SVVTGGYYYDGMDV	WGQGTTVTVSS
--------------------------------	VRIAGDYYYYYGMDV	WGQGTTVTVSS

FR3	CDR3	FR4
RFTISRDDSKNTLYLQMNSLKTE DTAVYYCTT		
-----------------------------F--S	TYSSGWYVWDYYGMDV	WGQGTTVTVSS
--------------------------E---I-	DRVLSYYAMAV	WGQGTTVTVSS

FR3	CDR3	FR4
RFTISRDNSKNTLYLQMNSLRAE DTAVYYCAK		
--------------------------------	SLIVVIVYALDH	WGQGTLVTVSS
--------------------------------	SLIVVIVYALDY	WGQGTLVTVSS
--------------------------------	SLIVVIVYALDY	WGQGTLVTVSS
--------------------------------	SLIVVMVYVLDY	WGQGTLVTVSS
--------------------------------	SLIVVMVYVLDY	WGQGTLVTVSS

FR3	CDR3	FR4
RFTISRDNSKNTLYLQMNSLRAE DTAVYYCAR		
--------------------------------	DRAAAGLHYYYGMDV	WGQGTTVTVSS
--------------------------------	DRAAAGLHYYYGMDV	WGQGTTVTVSS
--------------------------------	DRAAAGLHYYYGMDV	WGQGTTVTVSS

FR3	CDR3	FR4
RVTISVDTSKNQFSLKLSSVTAA DTAVYYCAR		
-----------------R--------------	ENIVVIPAAIFAGWFDP	WGQGTLVTVSS

FR3	CDR3	FR4
RVTISVDTSKNQFSLKLSSVTAA DTAVYYCAR		
---M-I--------------------------	DPDGDYYYYGMDV	WGQGTTVTVSS
---M-K-----------R--------------	DPDGDYYYYGMDV	WGQGTSVTVSS

FIG. 14

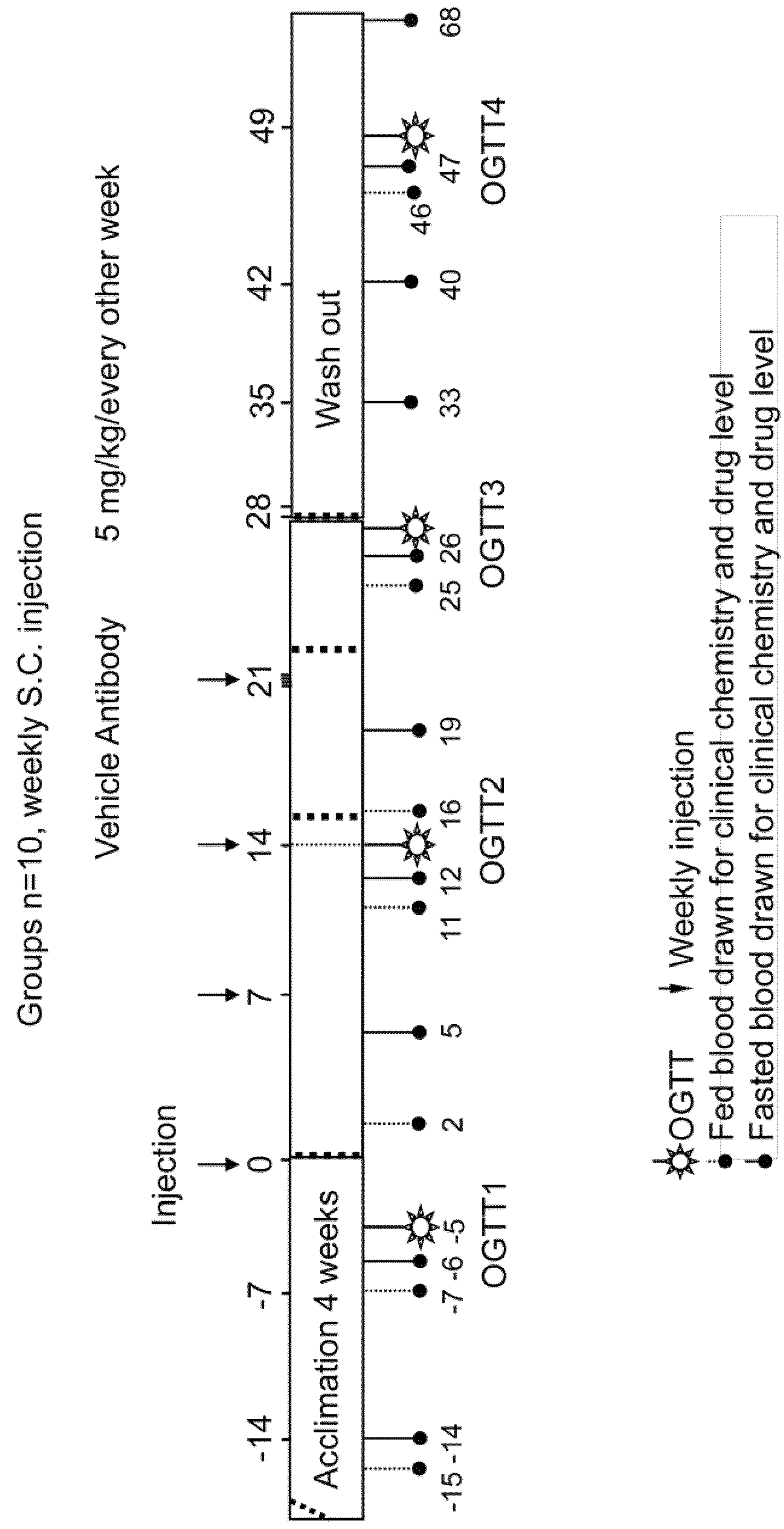

Groups n=10, weekly S.C. injection
Vehicle Antibody
5 mg/kg/every other week
Injection
-14
-7
0
7
14
21
28
35
42
49
Acclimation 4 weeks
Wash out
-15 -14
-7 -6 -5
2
5
11
12
16
19
25 26
33
40
46
47
68
OGTT1
OGTT2
OGTT3
OGTT4
OGTT
Weekly injection
Fed blood drawn for clinical chemistry and drug level
Fasted blood drawn for clinical chemistry and drug level

FIG. 15

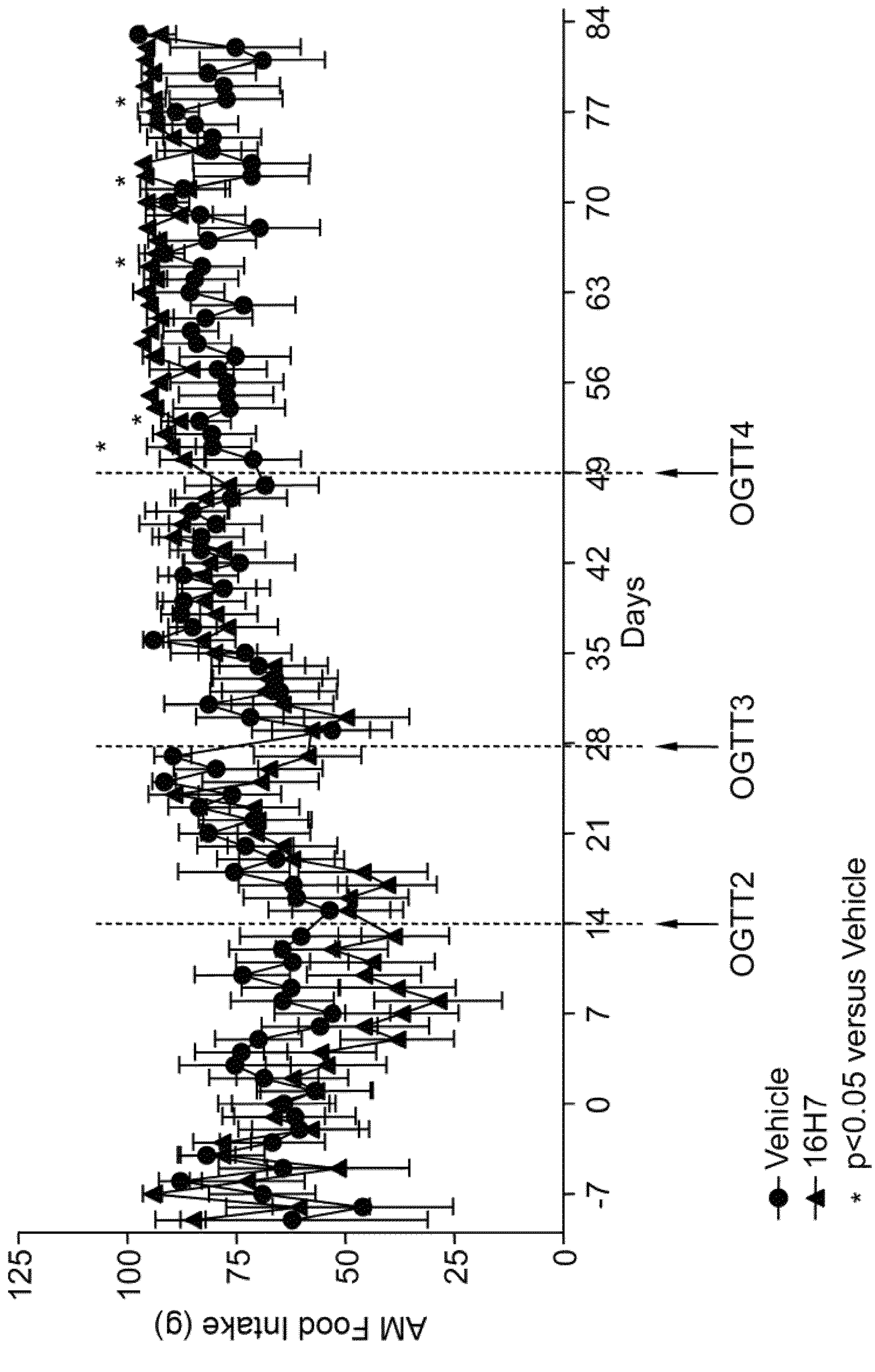

AM Food Intake (g)
125
100
75
50
25
0
-7
0
7
14
21
28
35
42
49
56
63
70
77
84
Days
OGTT2
OGTT3
OGTT4
Vehicle
16H7
* p<0.05 versus Vehicle

FIG. 16A

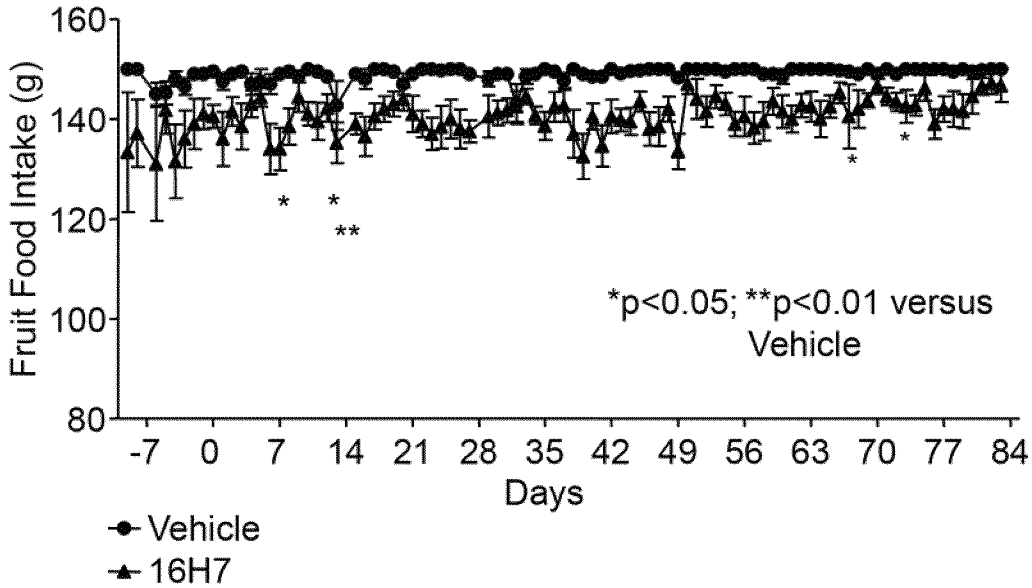


FIG. 16B

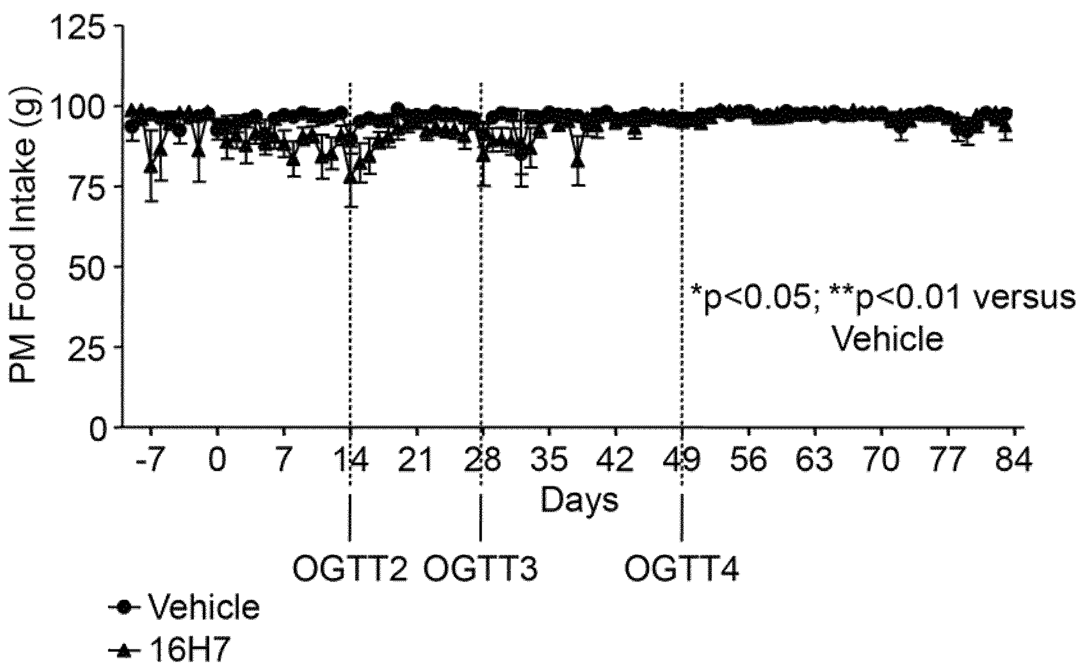


FIG. 17A

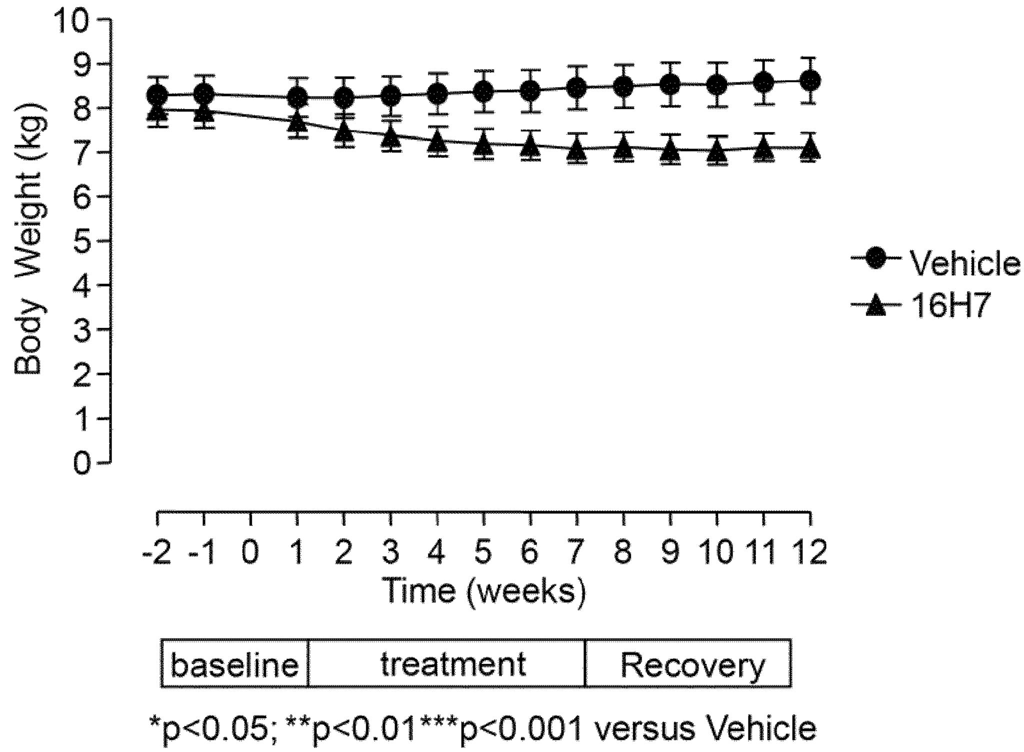


FIG. 17B

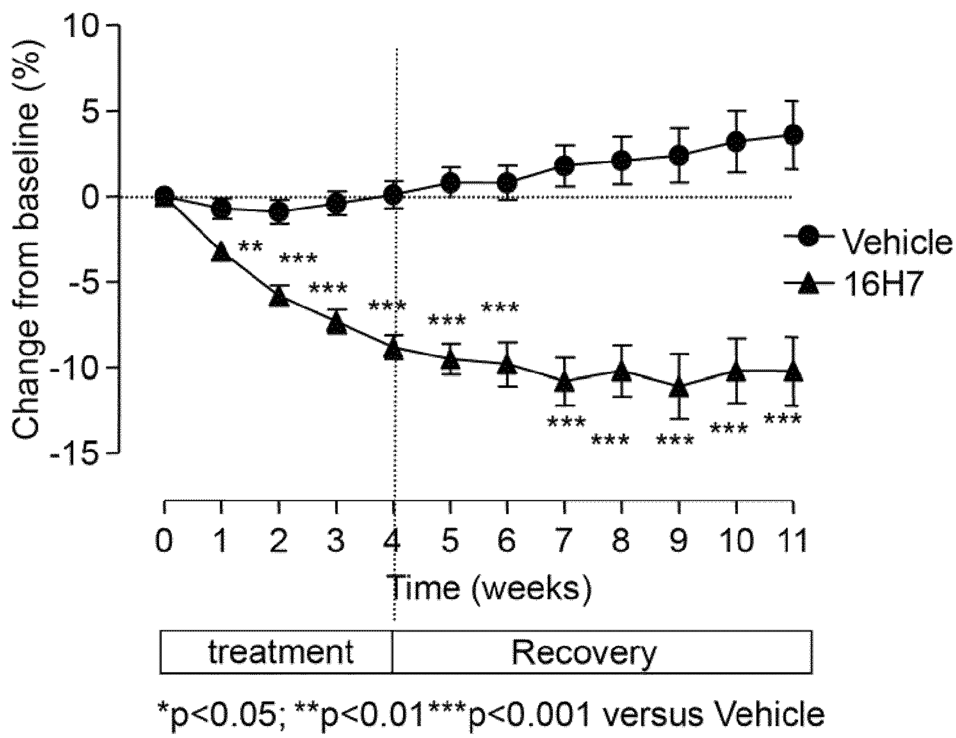


FIG. 18A

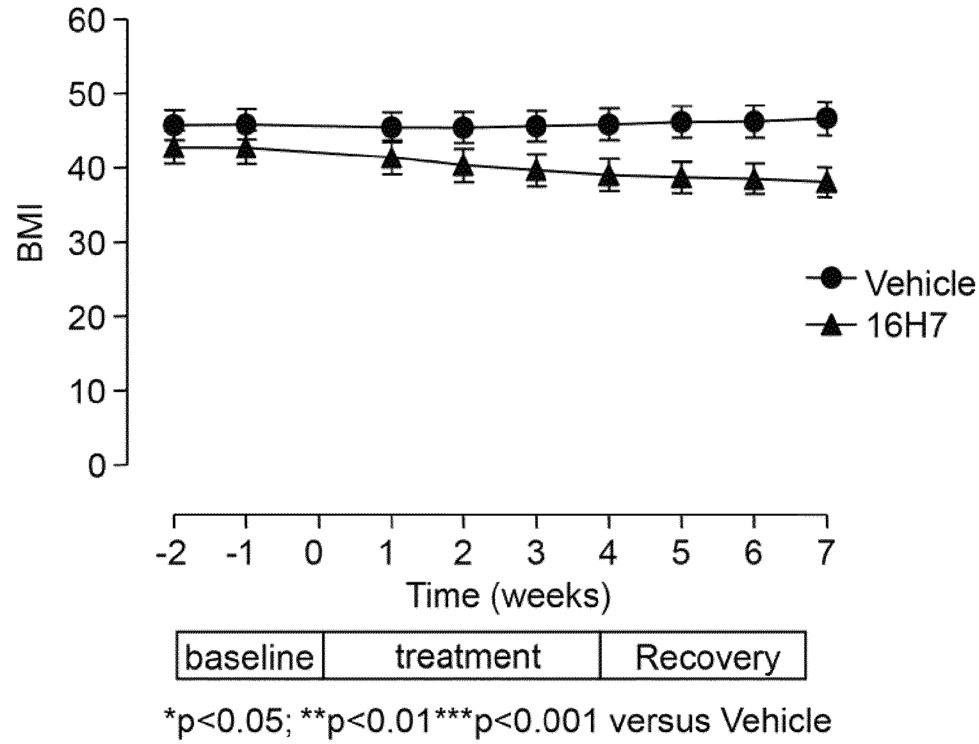


FIG. 18B

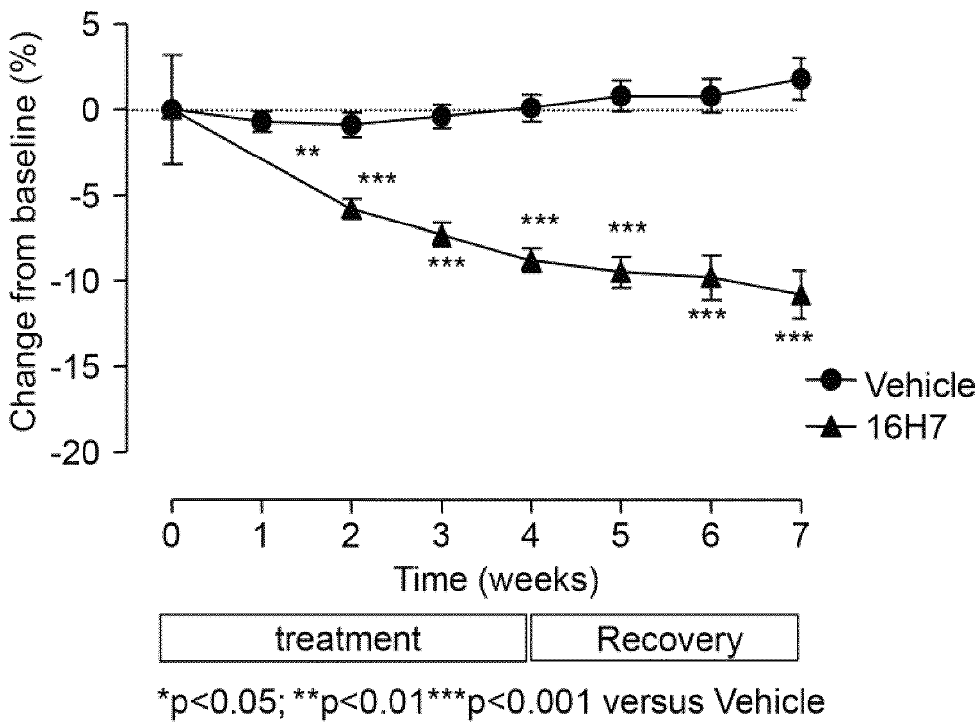
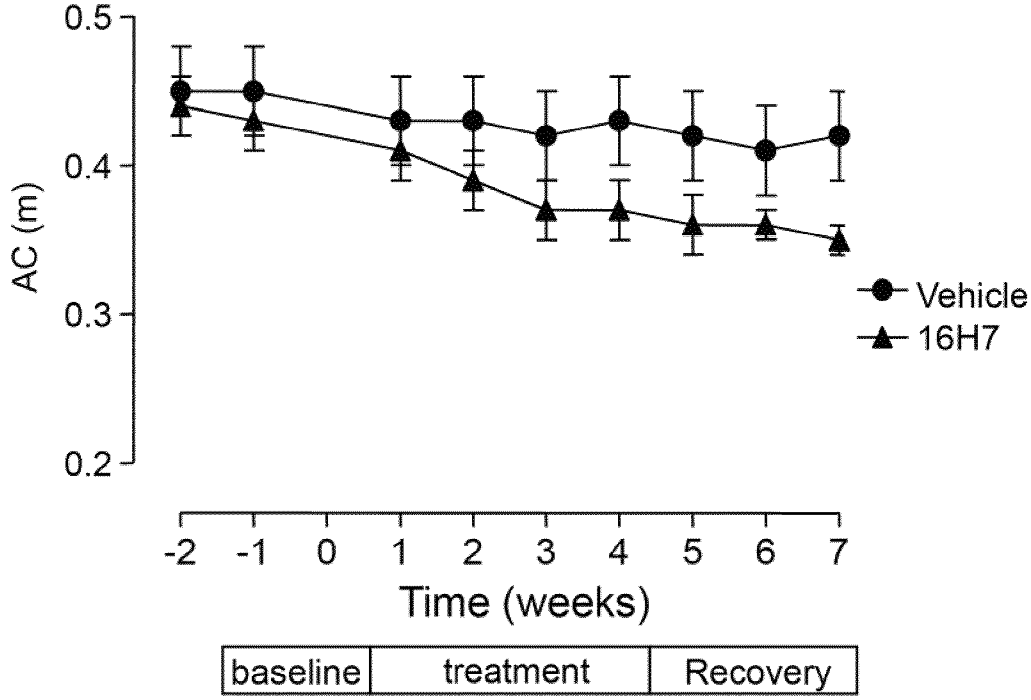
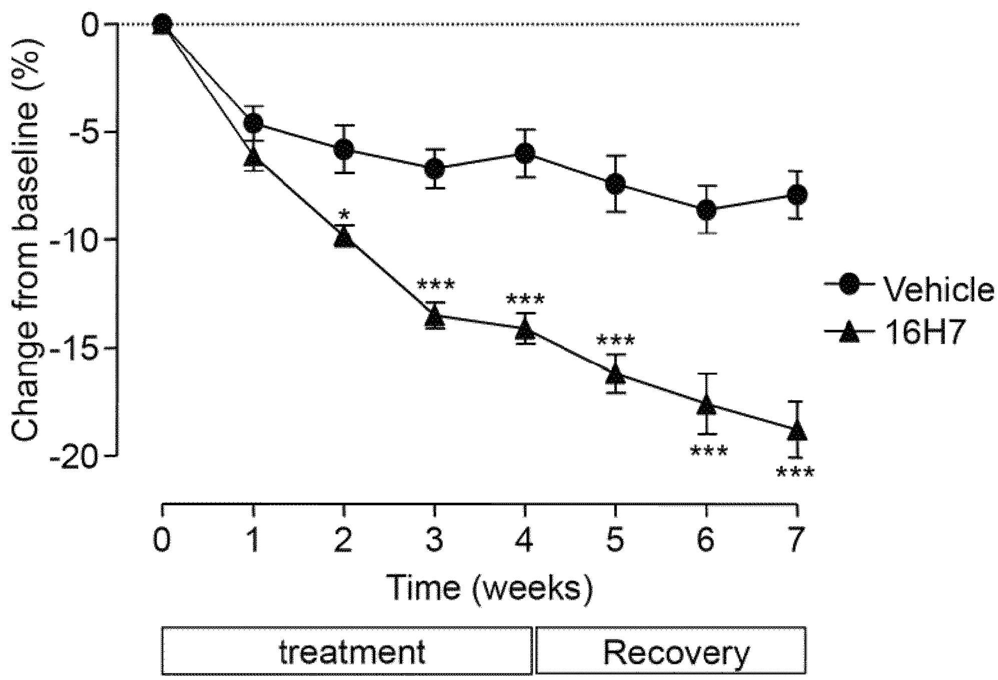


FIG. 19A



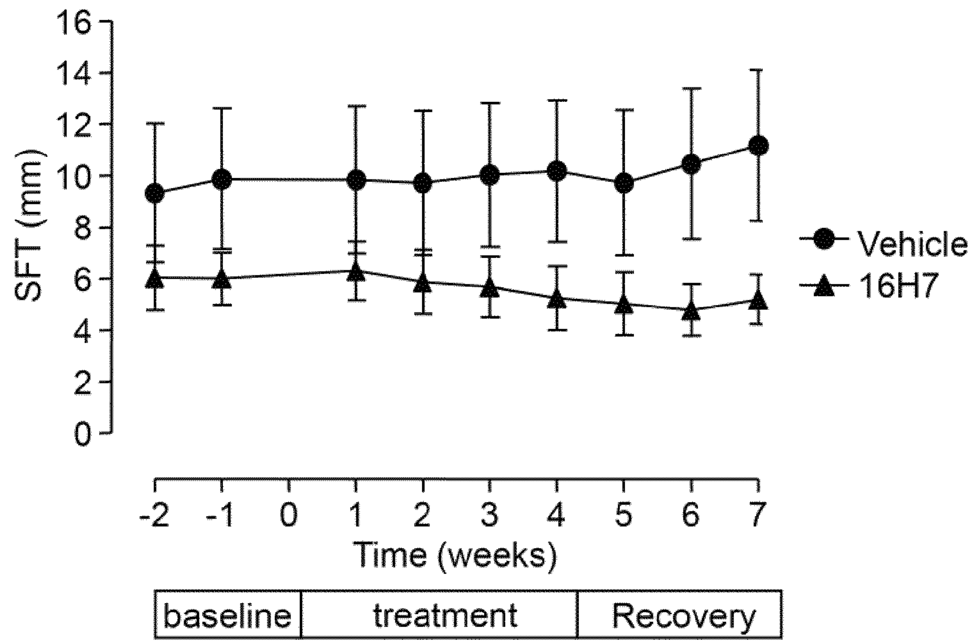
*p<0.05; **p<0.01***p<0.001 versus Vehicle

FIG. 19B



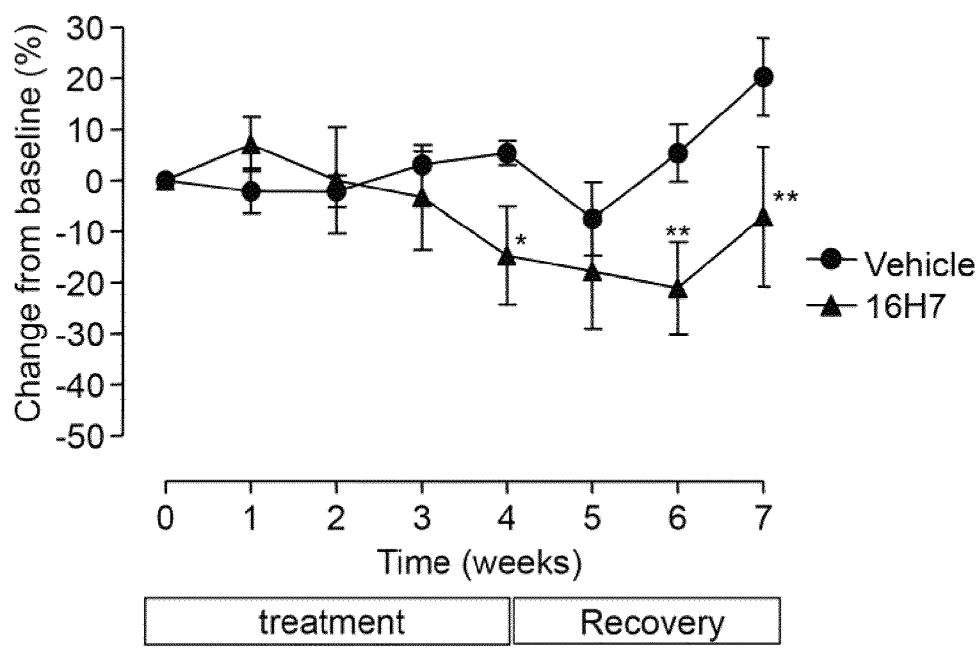
*p<0.05; **p<0.01***p<0.001 versus Vehicle

FIG. 20A



*p<0.05; **p<0.01***p<0.001 versus Vehicle

FIG. 20B



*p<0.05; **p<0.01***p<0.001 versus Vehicle

FIG. 21A

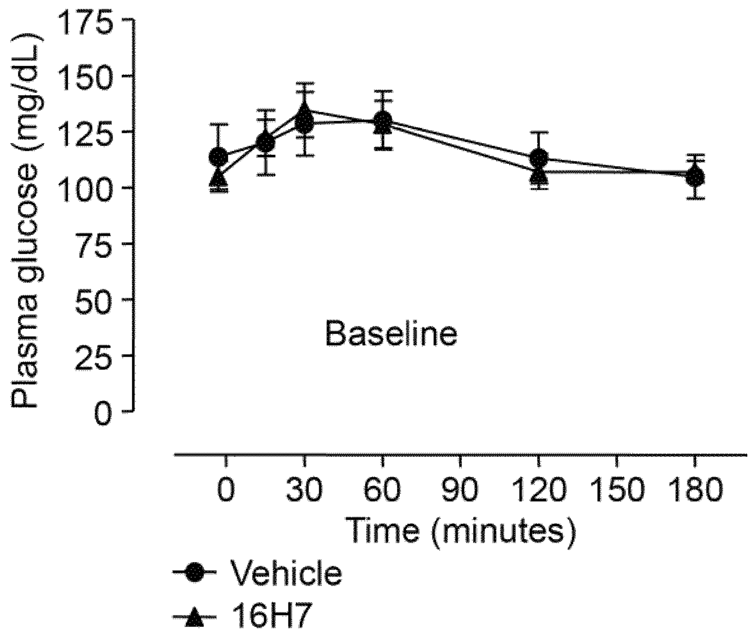


FIG. 21B

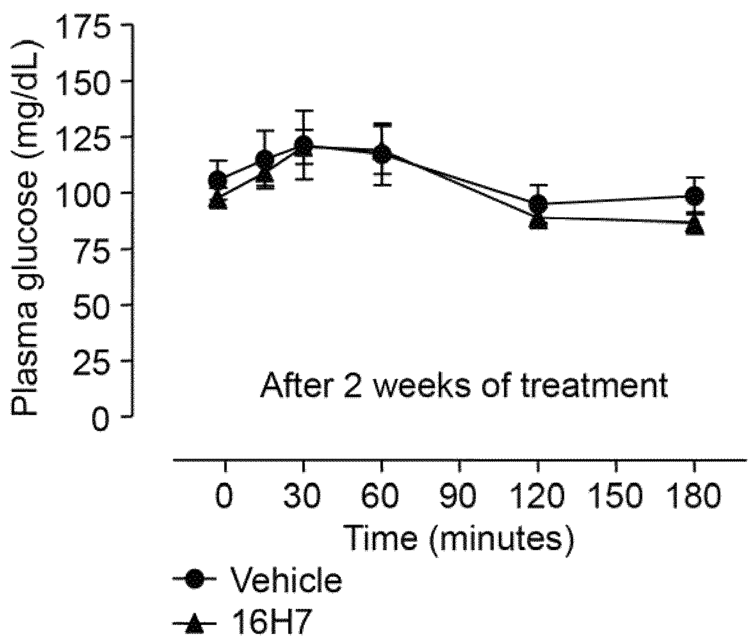


FIG. 21C

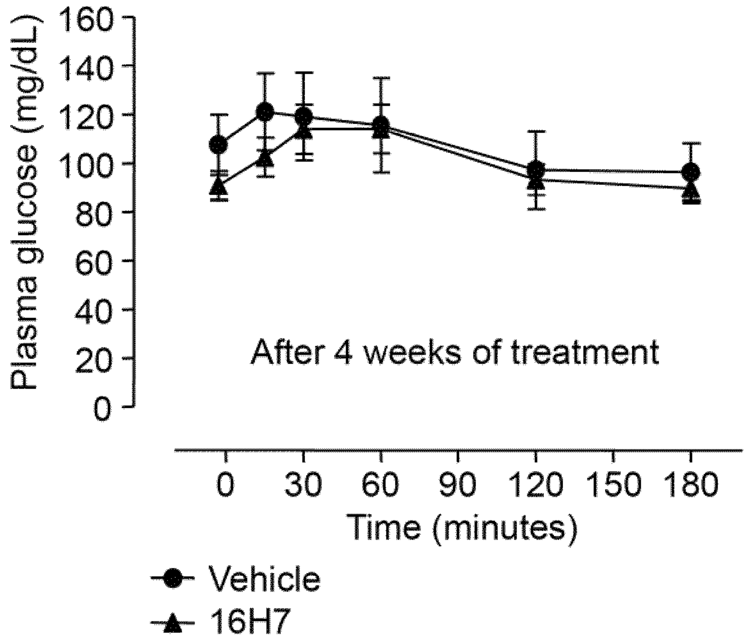


FIG. 21D

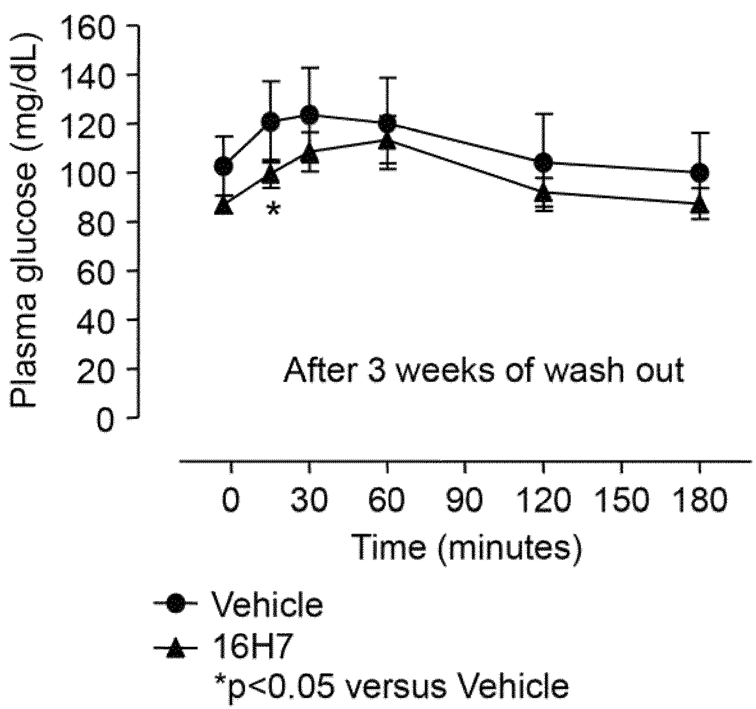


FIG. 22A

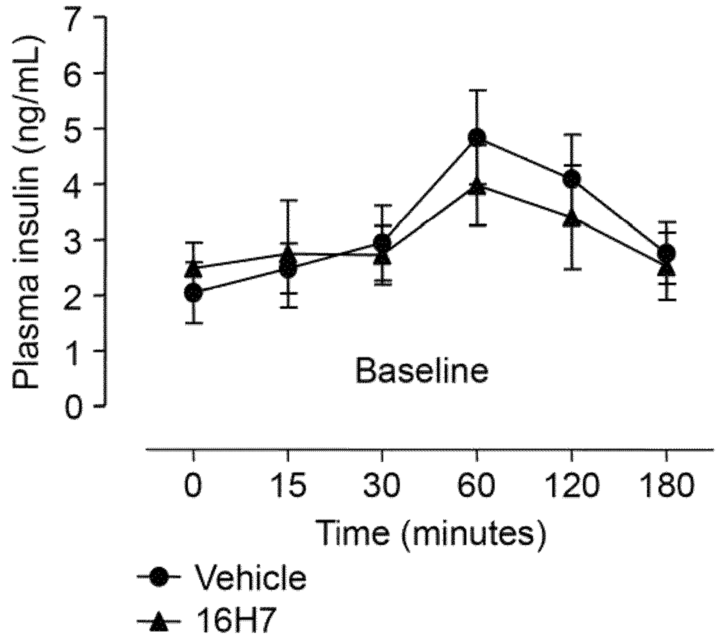


FIG. 22B

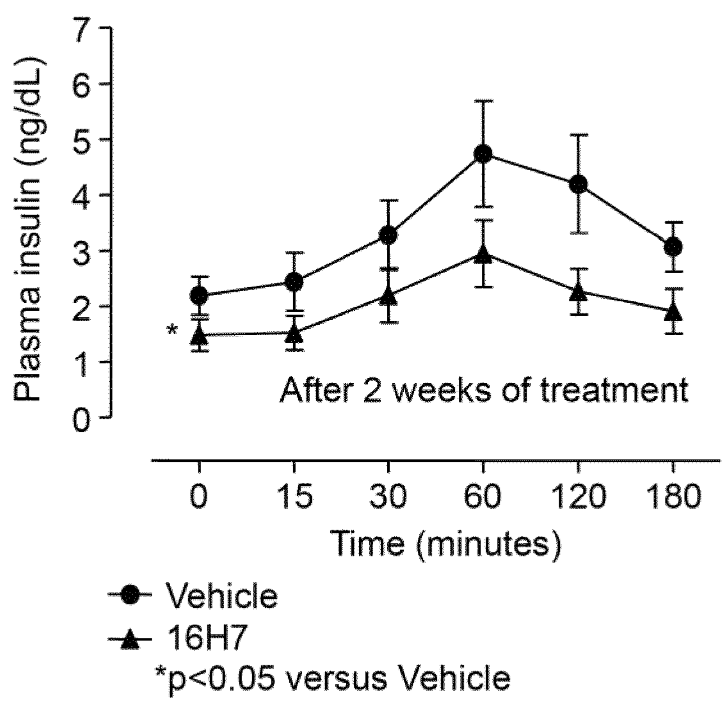


FIG. 22C

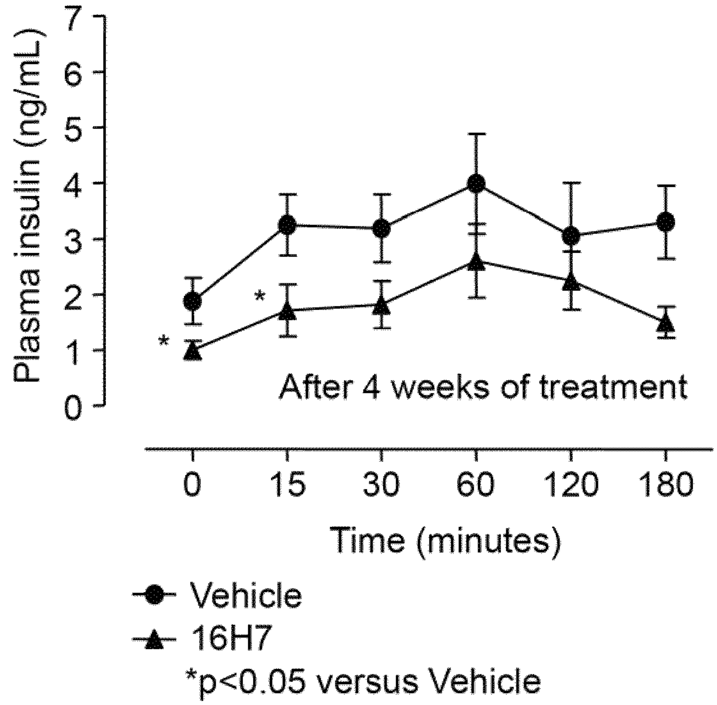


FIG. 22D

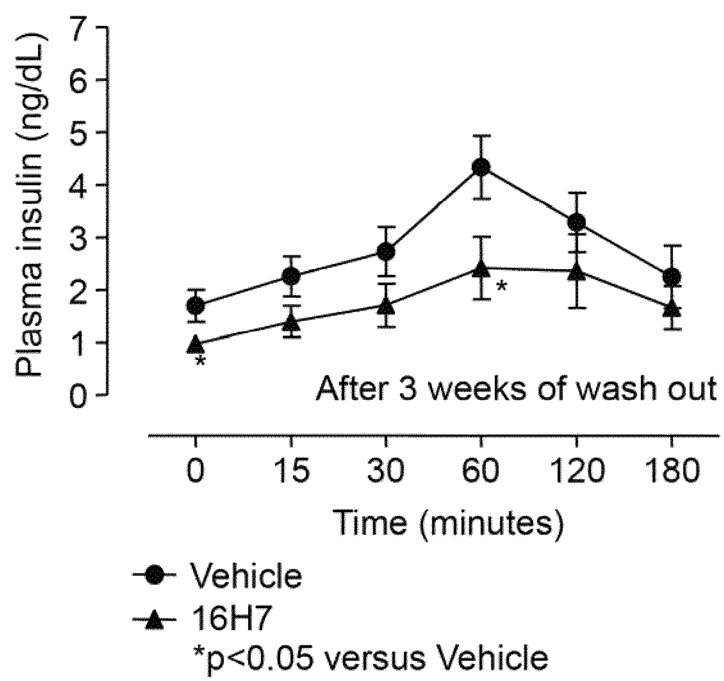


FIG. 23A

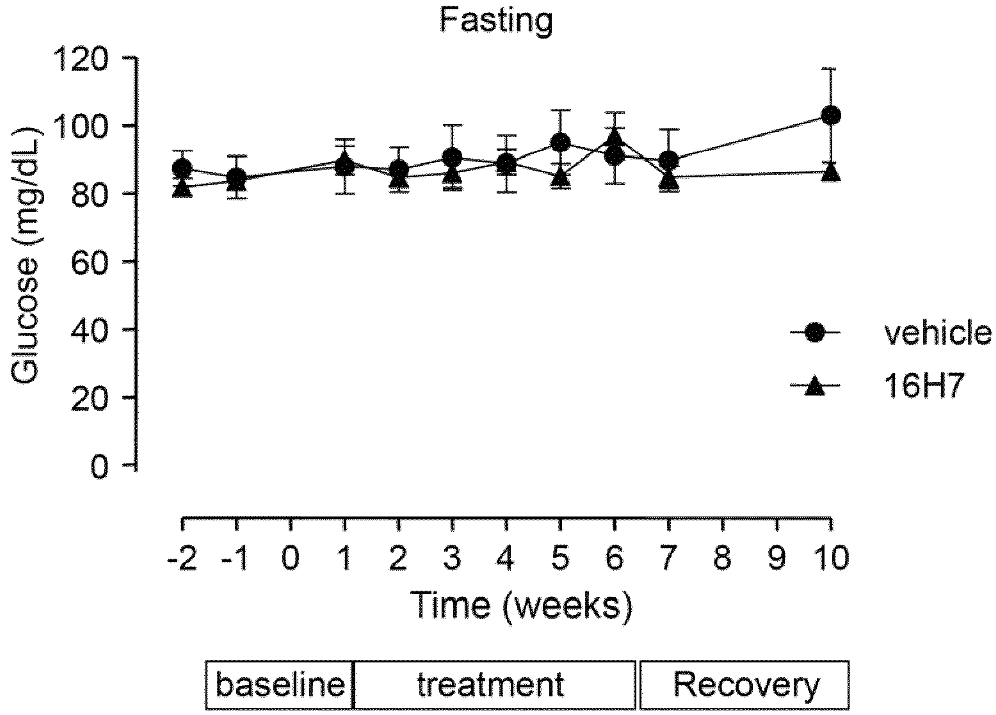


FIG. 23B

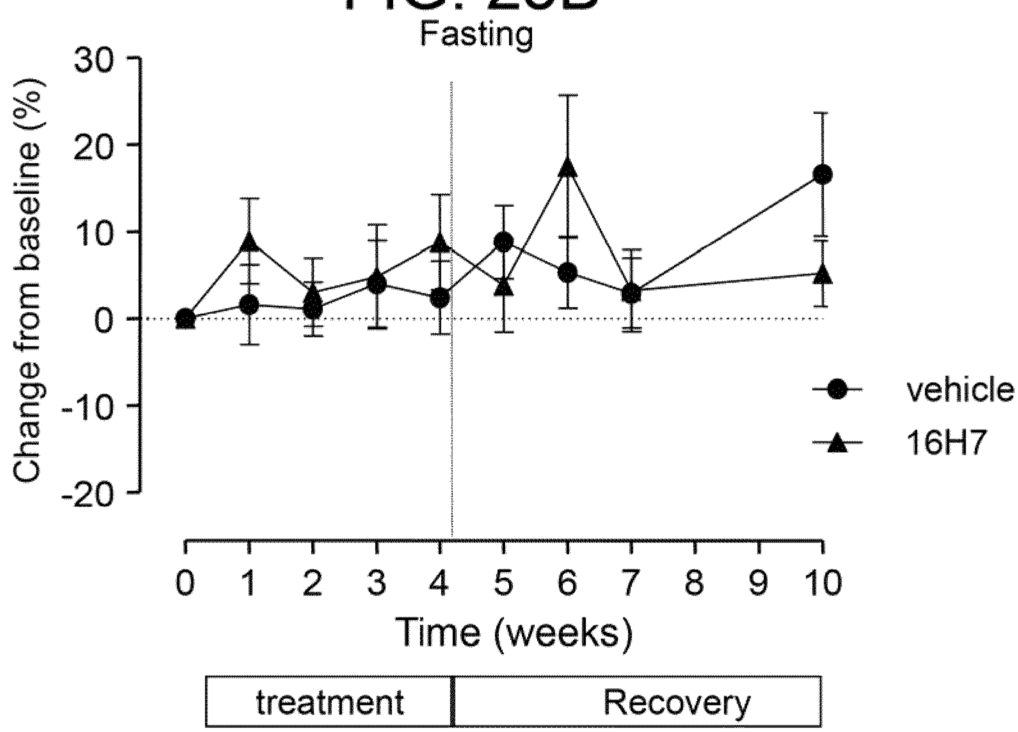


FIG. 24A

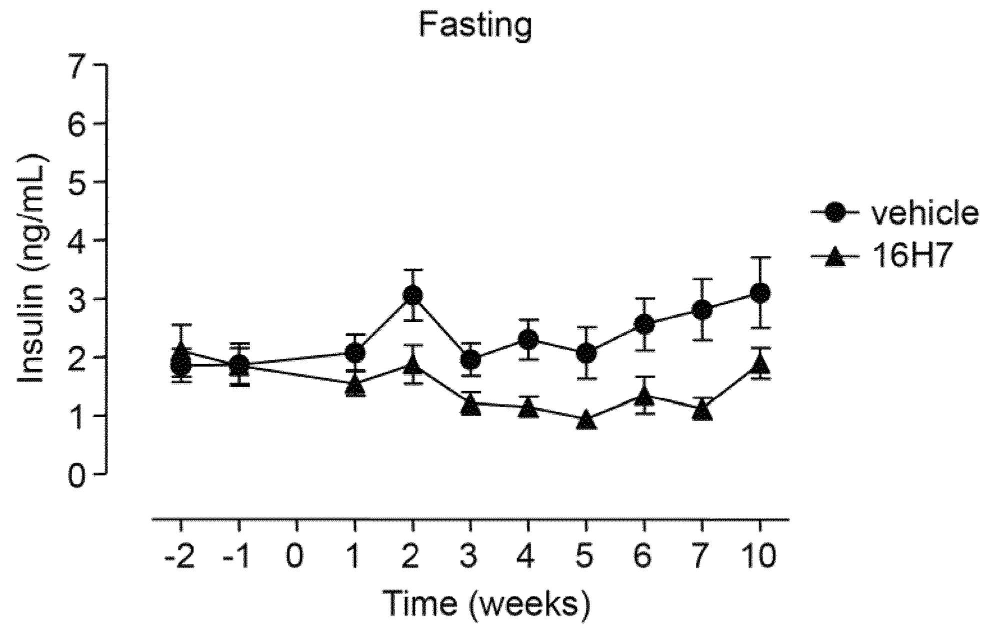


FIG. 24B

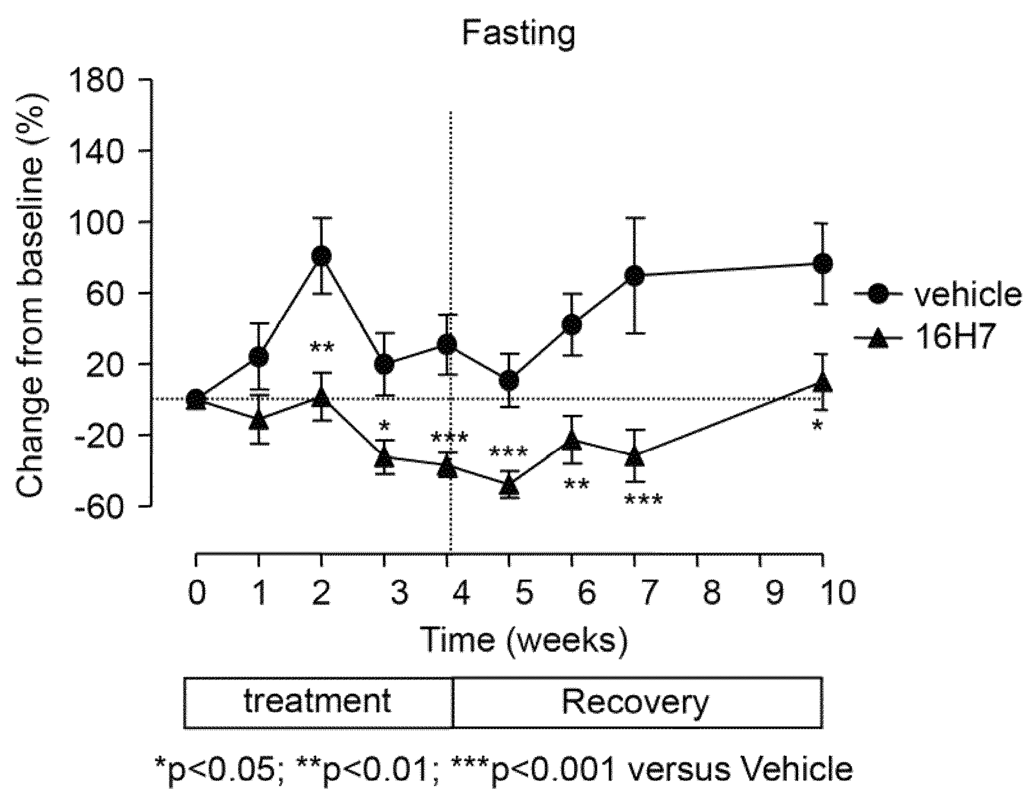
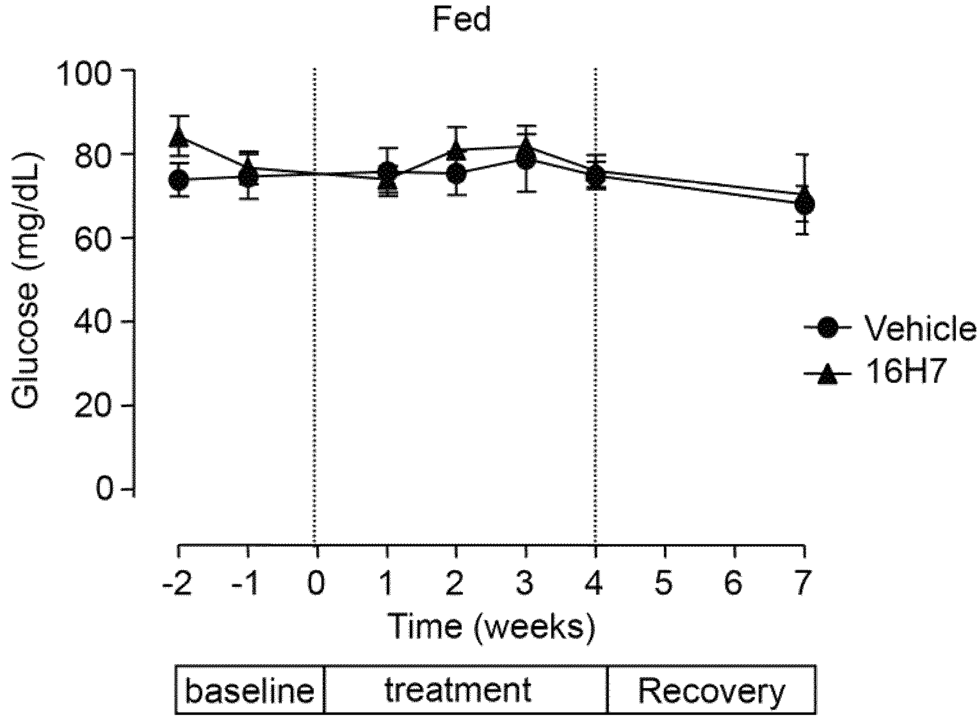


FIG. 25A



*p<0.05; **p<0.01; ***p<0.001 versus Vehicle

FIG. 25B

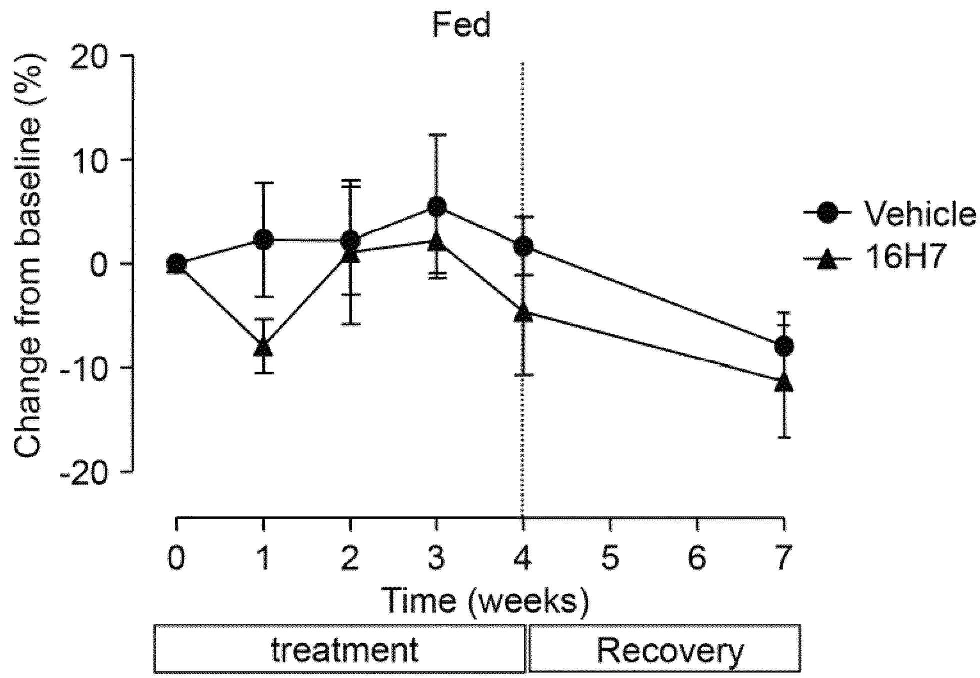
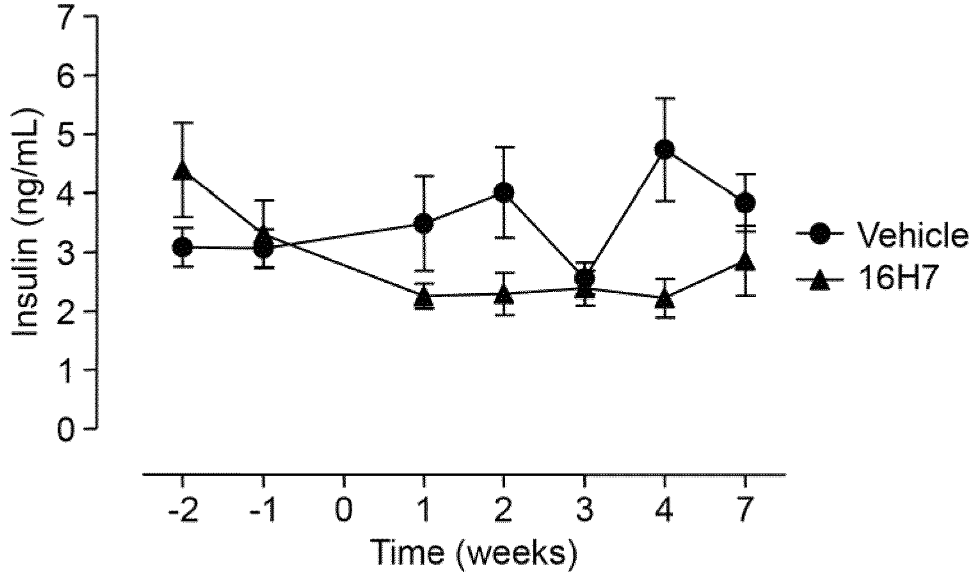


FIG. 26A



*p<0.05; **p<0.01; ***p<0.001 versus Vehicle

FIG. 26B

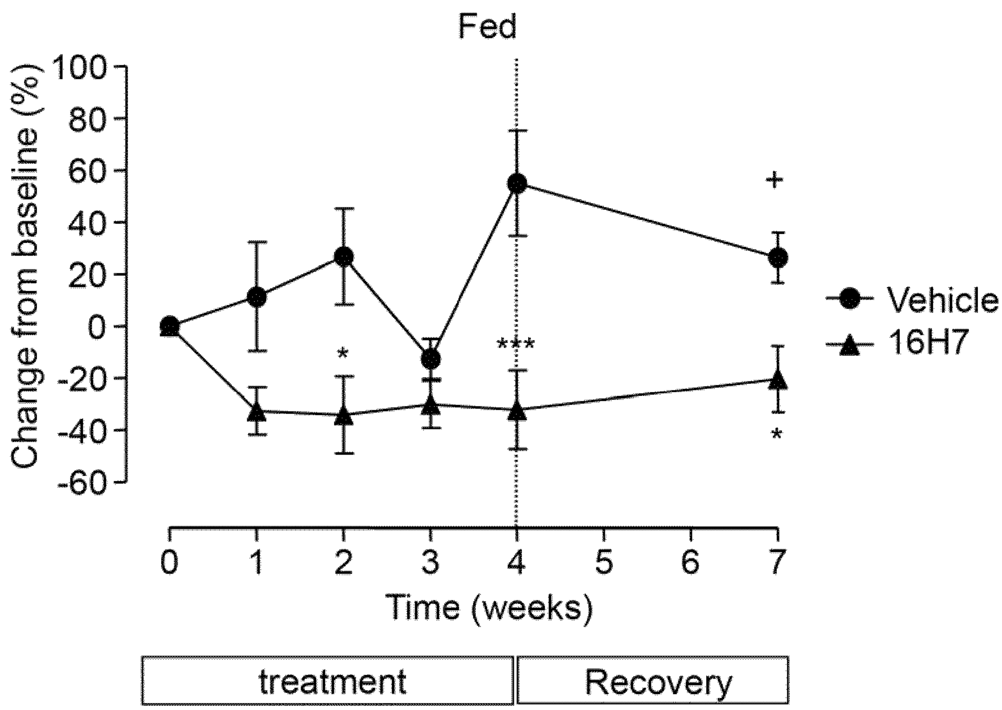
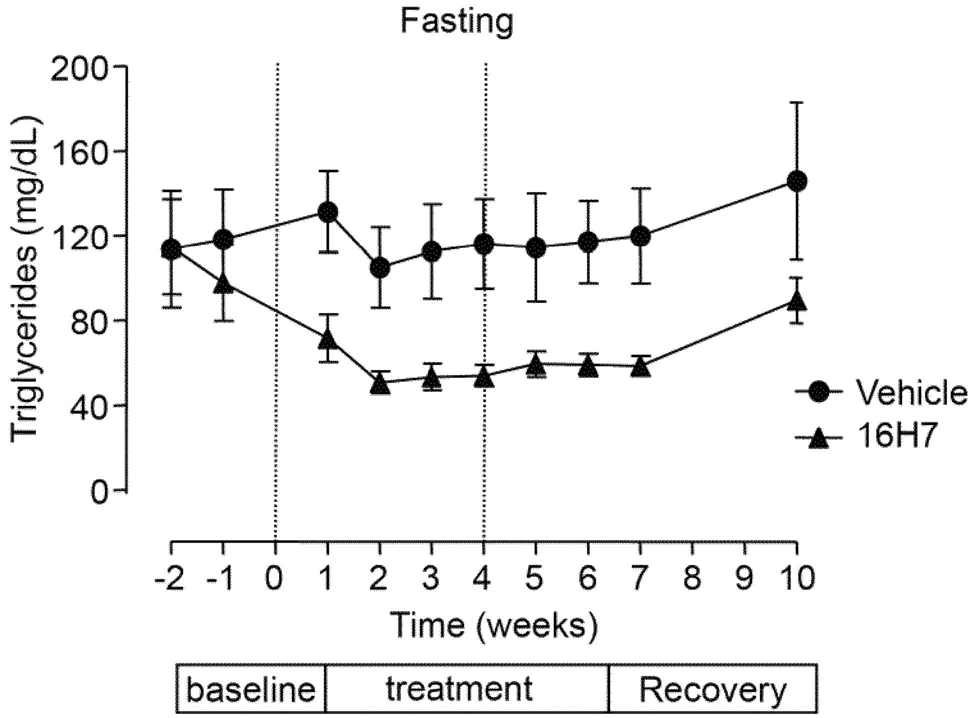


FIG. 27A



*p<0.05; **p<0.01; ***p<0.001 versus Vehicle

FIG. 27B

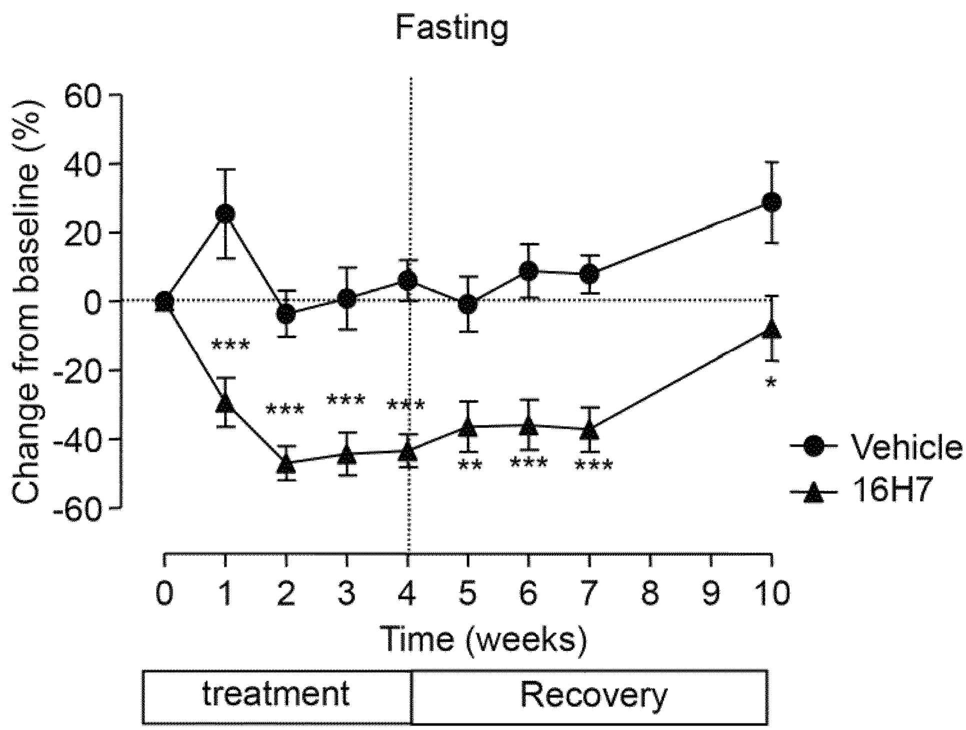
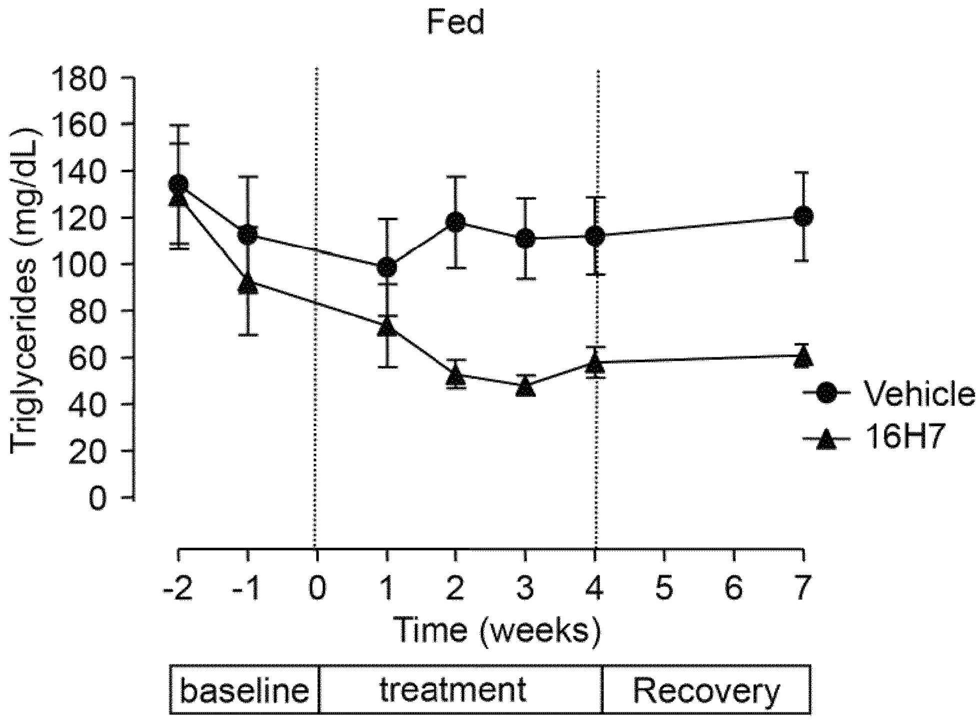


FIG. 28A



*p<0.05; **p<0.01; ***p<0.001 versus Vehicle

FIG. 28B

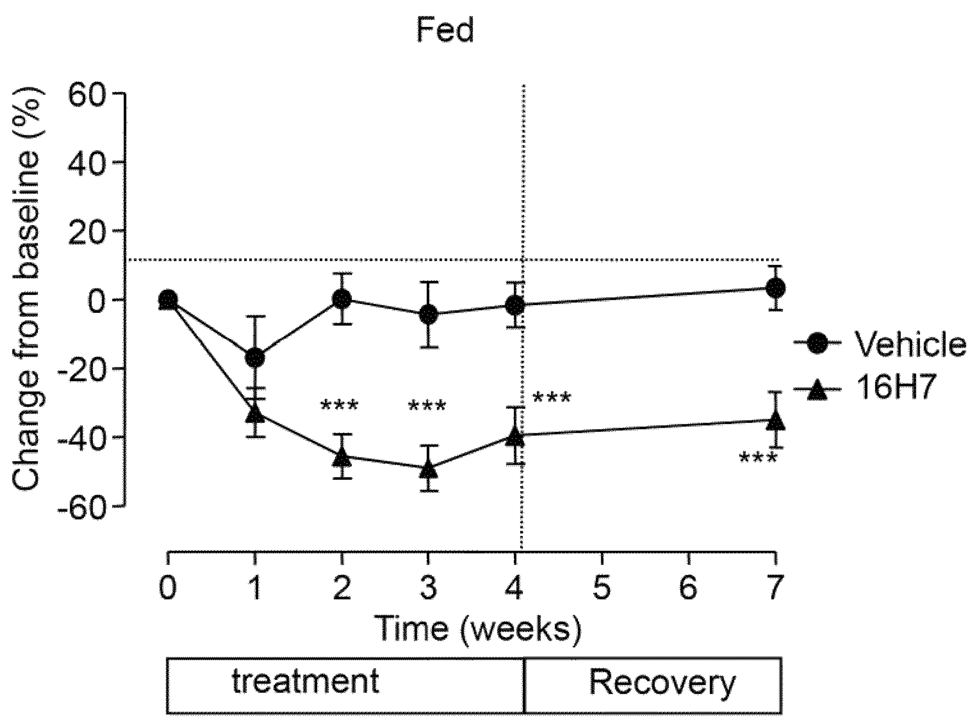
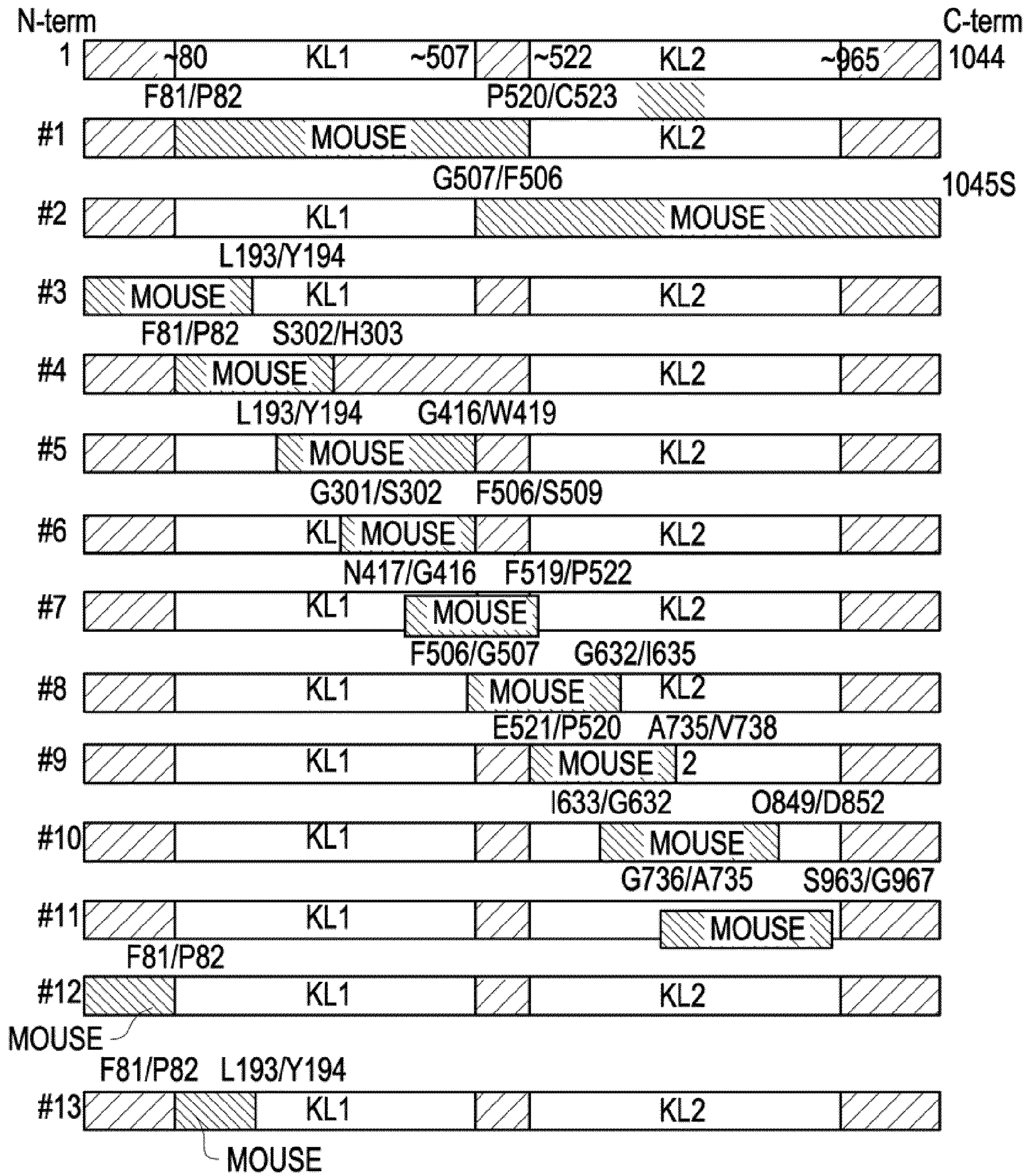


FIG. 29


N-term
C-term
1
~80
KL1
~507
~522
KL2
~965
1044
F81/P82
P520/C523
#1
MOUSE
KL2
G507/F506
1045S
#2
KL1
MOUSE
L193/Y194
#3
MOUSE
KL1
KL2
F81/P82
S302/H303
#4
MOUSE
KL2
L193/Y194
G416/W419
#5
MOUSE
KL2
G301/S302
F506/S509
#6
KL
MOUSE
KL2
N417/G416
F519/P522
#7
KL1
MOUSE
KL2
F506/G507
G632/I635
#8
KL1
MOUSE
KL2
E521/P520
A735/V738
#9
KL1
MOUSE
2
I633/G632
O849/D852
#10
KL1
MOUSE
G736/A735
S963/G967
#11
KL1
MOUSE
F81/P82
#12
KL1
KL2
MOUSE
F81/P82
L193/Y194
#13
KL1
KL2
MOUSE

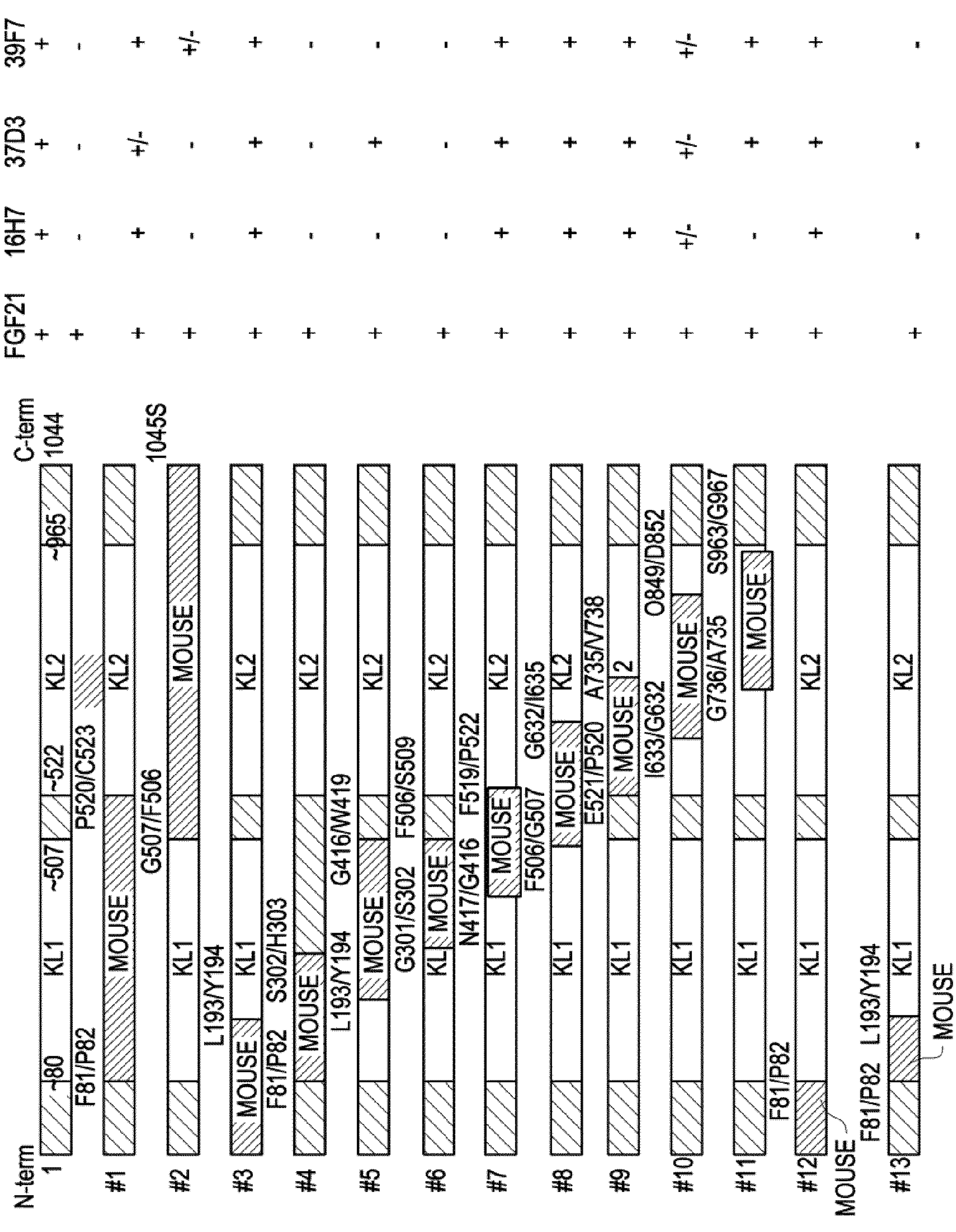

N-term
C-term
1
~80
KL1
~507
~522
KL2
~965
1044
1045S
FGF21
16H7
37D3
39F7
#1
#2
#3
#4
#5
#6
#7
#8
#9
#10
#11
#12
#13
MOUSE
F81/P82
P520/C523
G507/F506
L193/Y194
S302/H303
G416/W419
G301/S302
F506/S509
N417/G416
F519/P522
F506/G507
G632/I635
E521/P520
A735/V738
I633/G632
O849/D852
G736/A735
S963/G967

FIG. 30

FIG. 31A

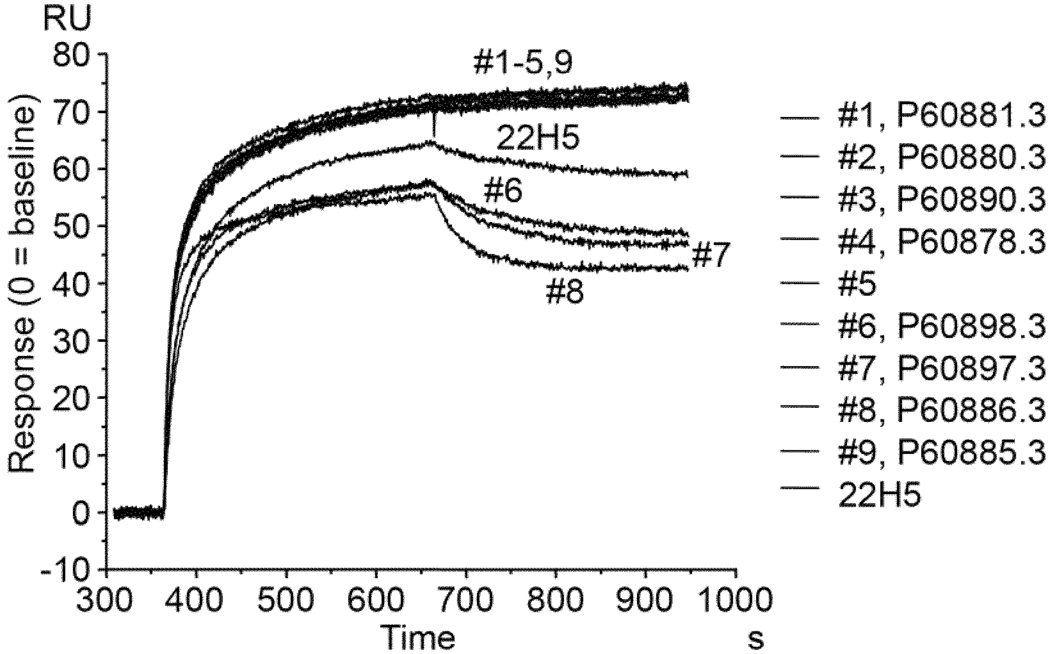


FIG. 31B

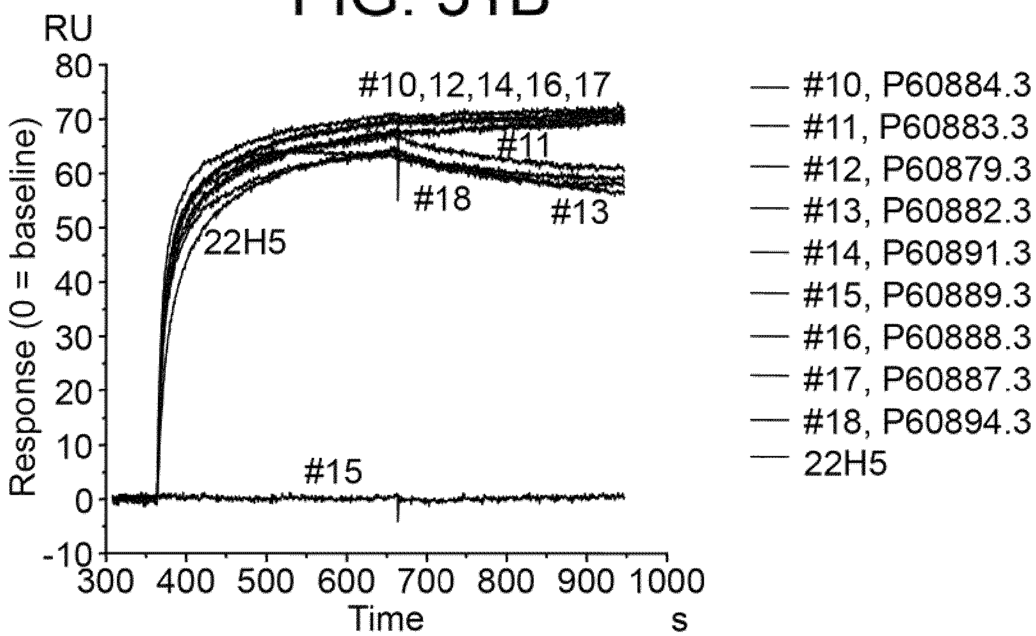


FIG. 31C

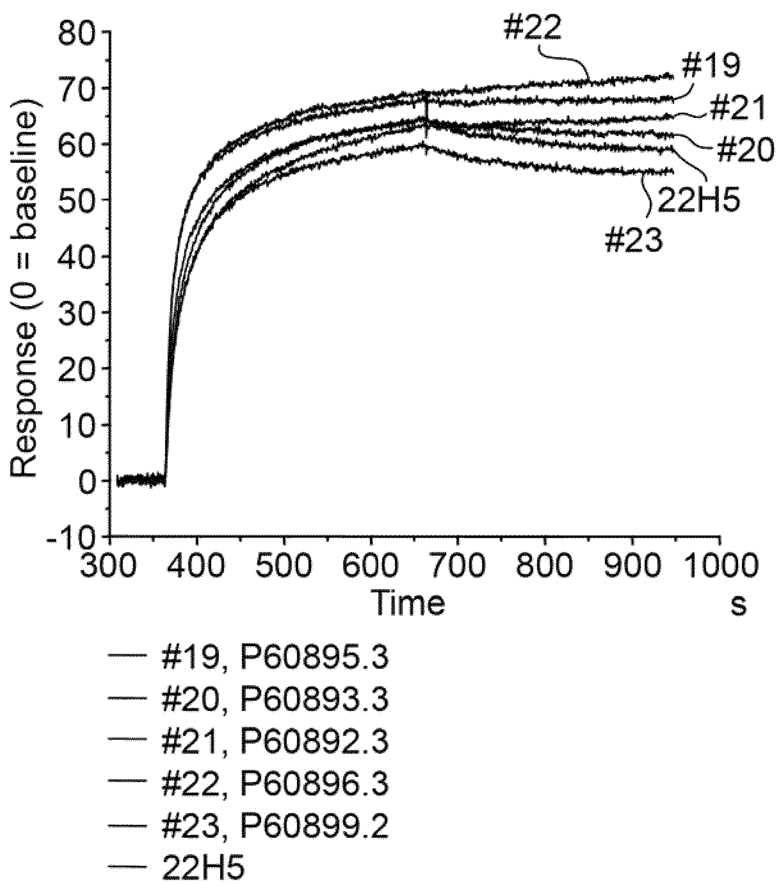
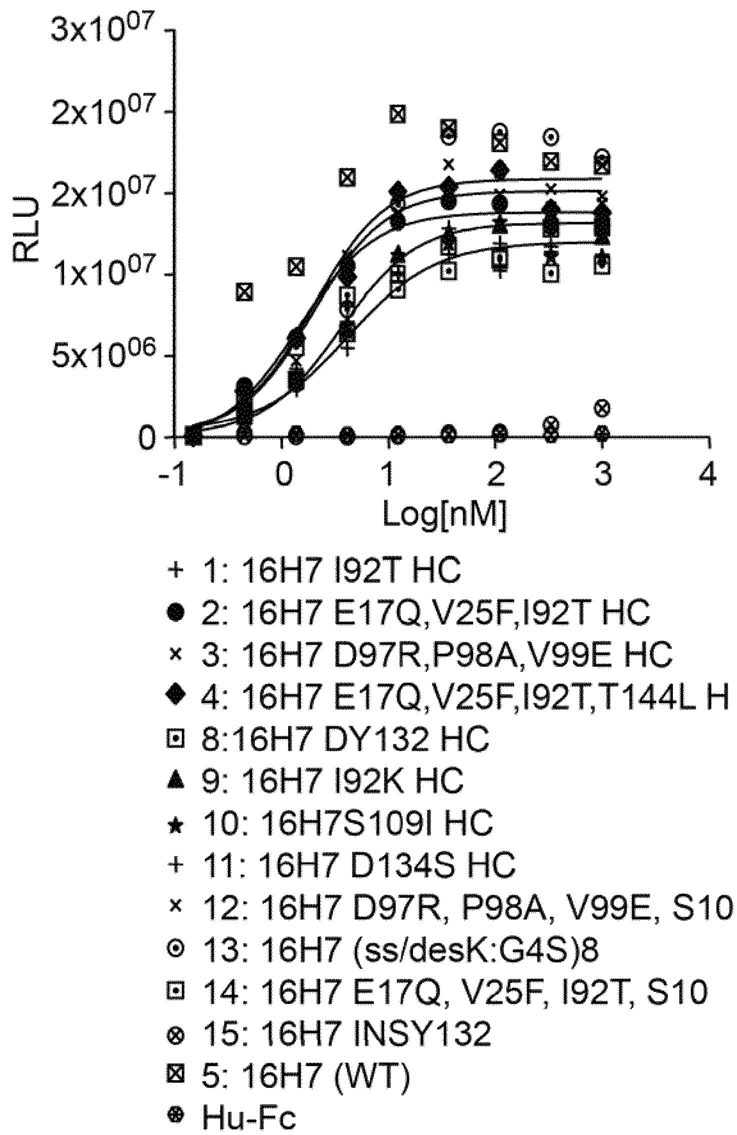

80
70
60
50
40
30
20
10
0
-10
Response (0 = baseline)
300
400
500
600
700
800
900
1000
Time
s
#22
#19
#21
#20
22H5
#23
— #19, P60895.3
— #20, P60893.3
— #21, P60892.3
— #22, P60896.3
— #23, P60899.2
— 22H5

FIG. 32A



3x10^07
2x10^07
2x10^07
1x10^07
5x10^06
0
RLU
-1
0
1
2
3
4
Log[nM]
1: 16H7 I92T HC
2: 16H7 E17Q,V25F,I92T HC
3: 16H7 D97R,P98A,V99E HC
4: 16H7 E17Q,V25F,I92T,T144L H
8:16H7 DY132 HC
9: 16H7 I92K HC
10: 16H7S109I HC
11: 16H7 D134S HC
12: 16H7 D97R, P98A, V99E, S10
13: 16H7 (ss/desK:G4S)8
14: 16H7 E17Q, V25F, I92T, S10
15: 16H7 INSY132
5: 16H7 (WT)
Hu-Fc

FIG. 32B

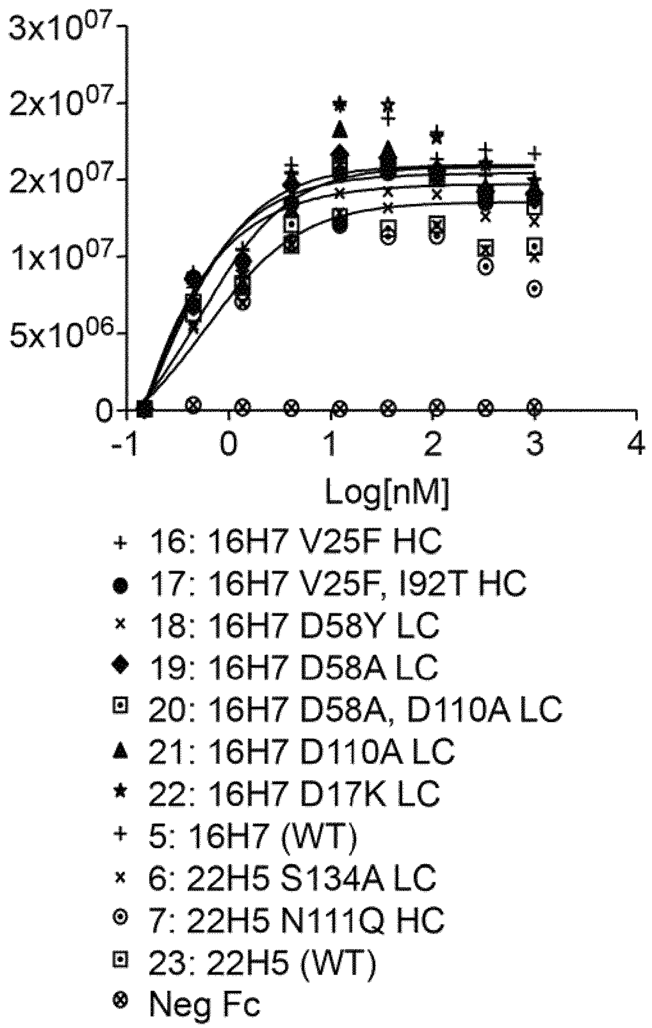

3x10^07
2x10^07
2x10^07
1x10^07
5x10^06
0
-1
0
1
2
3
4
Log[nM]
16: 16H7 V25F HC
17: 16H7 V25F, I92T HC
18: 16H7 D58Y LC
19: 16H7 D58A LC
20: 16H7 D58A, D110A LC
21: 16H7 D110A LC
22: 16H7 D17K LC
5: 16H7 (WT)
6: 22H5 S134A LC
7: 22H5 N111Q HC
23: 22H5 (WT)
Neg Fc

FIG. 32C

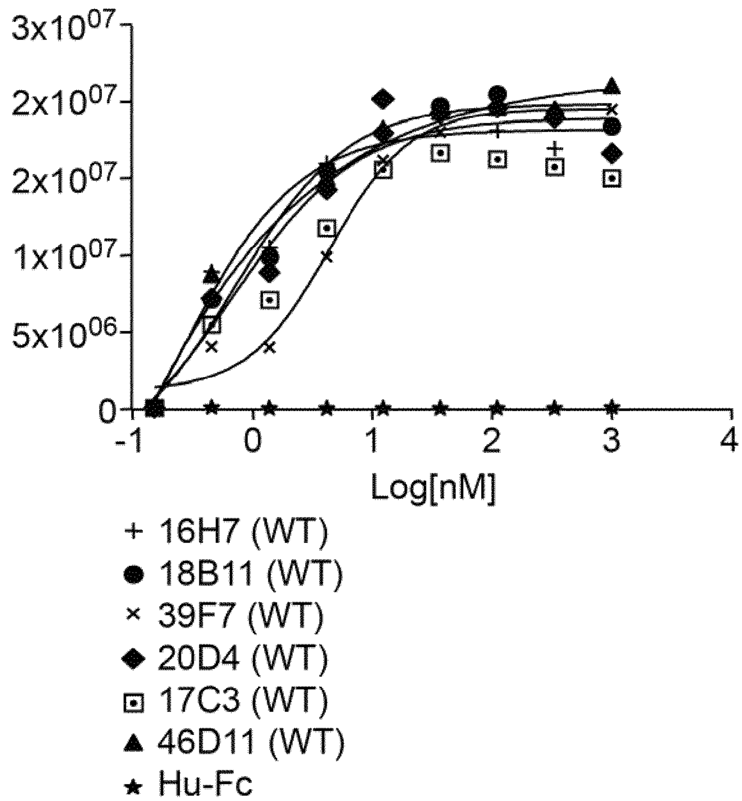
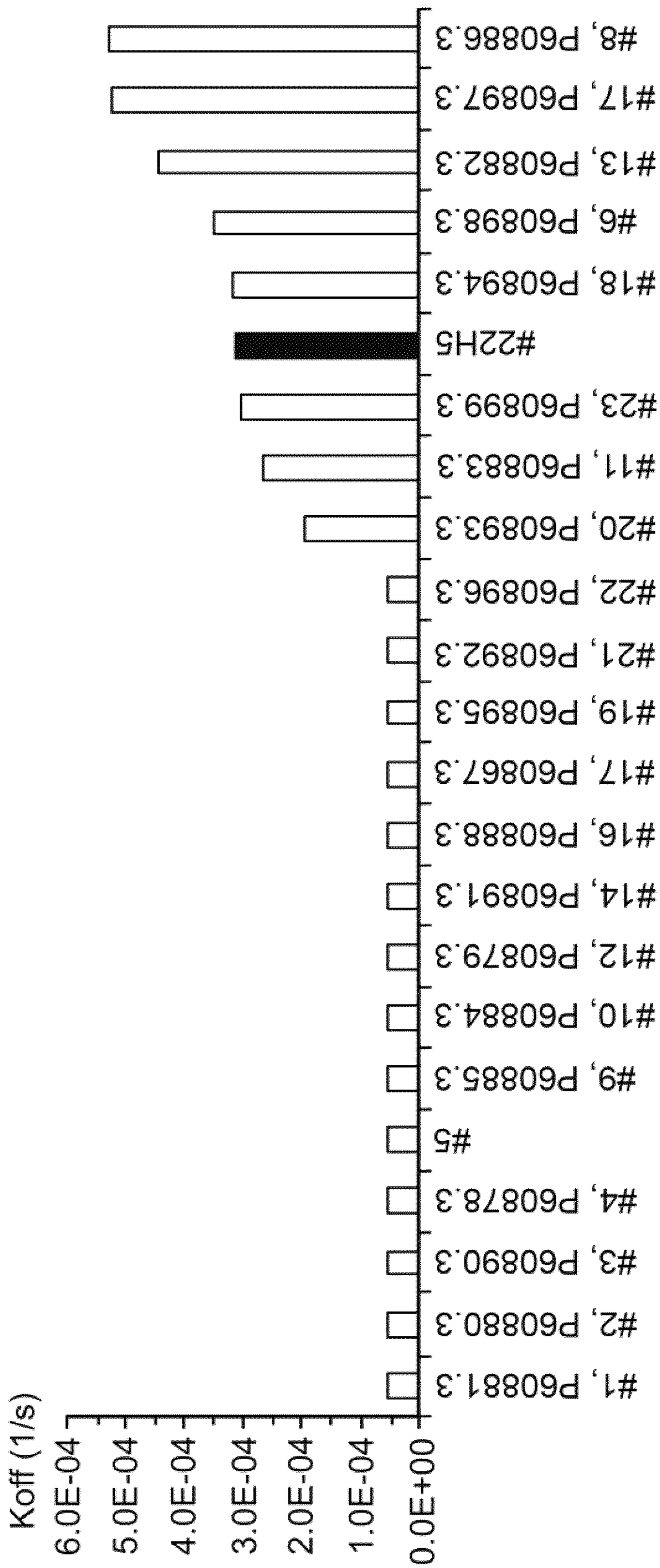

3x10^07
2x10^07
2x10^07
1x10^07
5x10^06
0
-1
0
1
2
3
4
Log[nM]
16H7 (WT)
18B11 (WT)
39F7 (WT)
20D4 (WT)
17C3 (WT)
46D11 (WT)
Hu-Fc

FIG. 33



Koff (1/s)
6.0E-04
5.0E-04
4.0E-04
3.0E-04
2.0E-04
1.0E-04
0.0E+00
#1, P60881.3
#2, P60880.3
#3, P60890.3
#4, P60878.3
#5
#9, P60885.3
#10, P60884.3
#12, P60879.3
#14, P60891.3
#16, P60888.3
#17, P60867.3
#19, P60895.3
#21, P60892.3
#22, P60896.3
#20, P60893.3
#11, P60883.3
#23, P60899.3
#22H5
#18, P60894.3
#6, P60898.3
#13, P60882.3
#17, P60897.3
#8, P60886.3

FIG. 34A

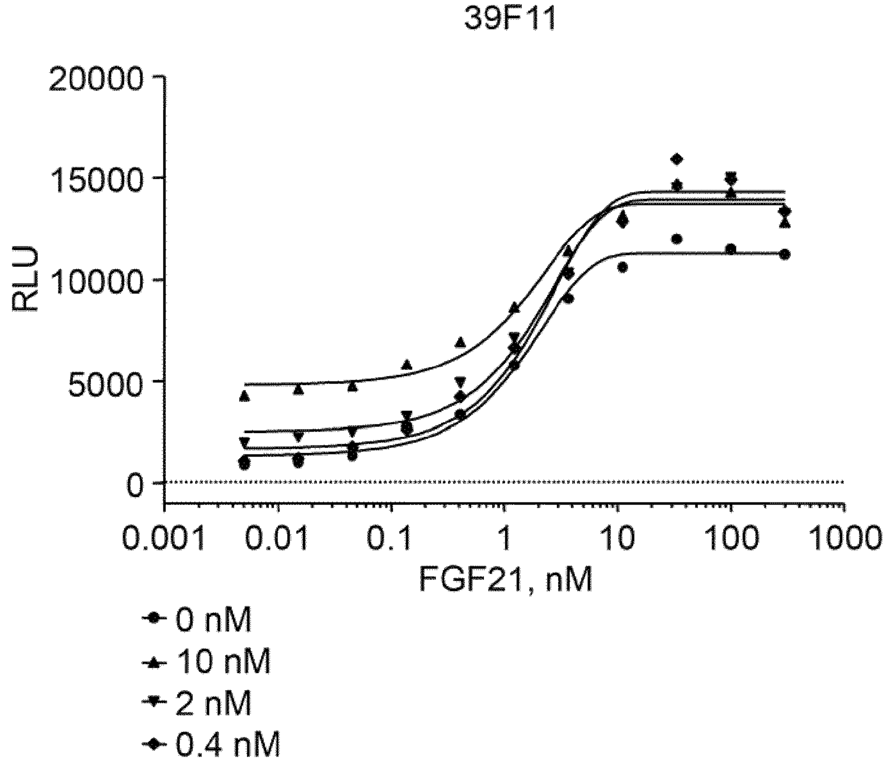


FIG. 34B

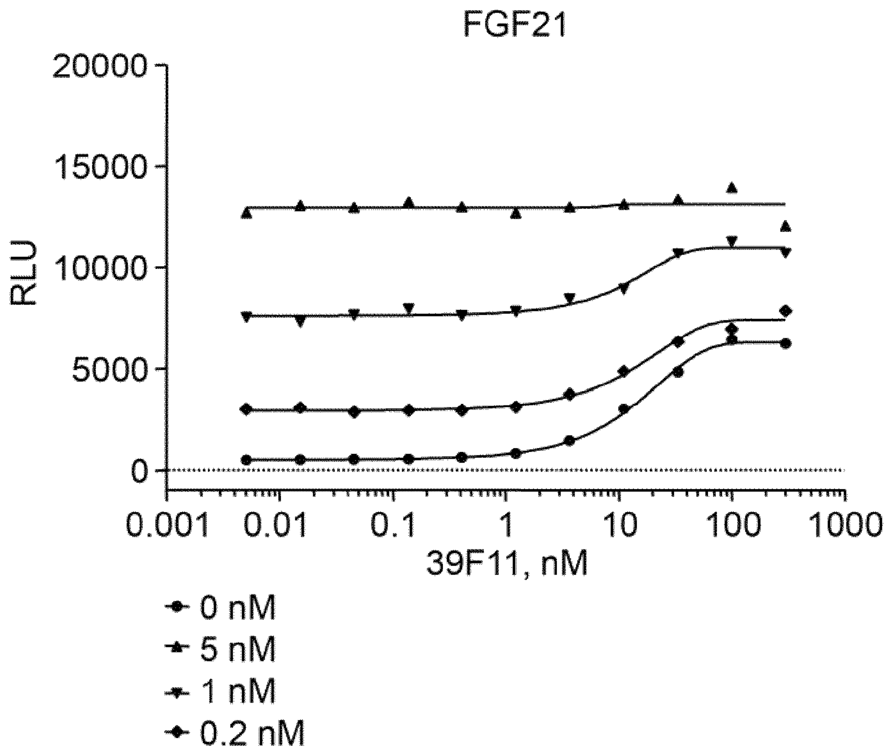


FIG. 35A

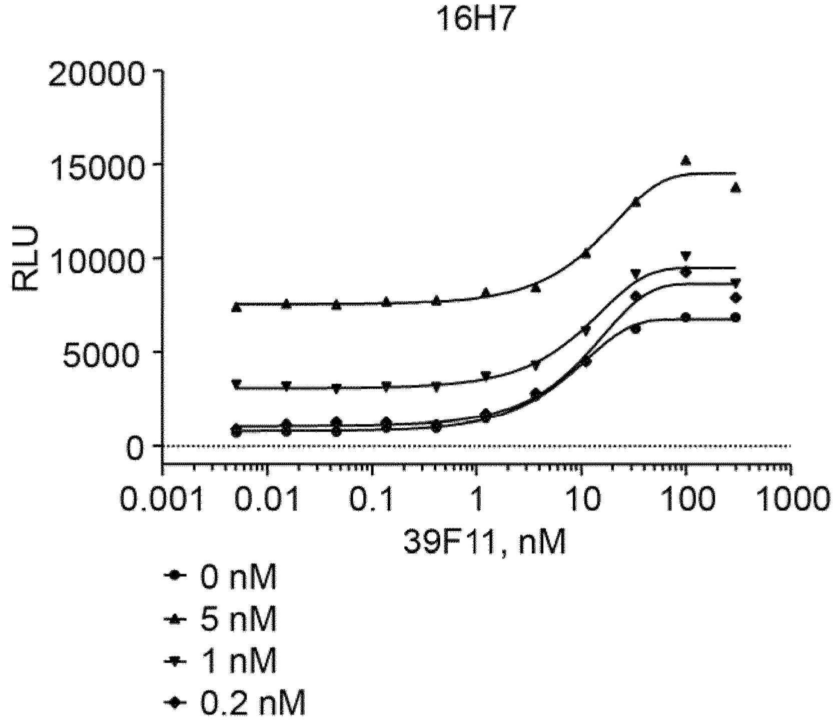
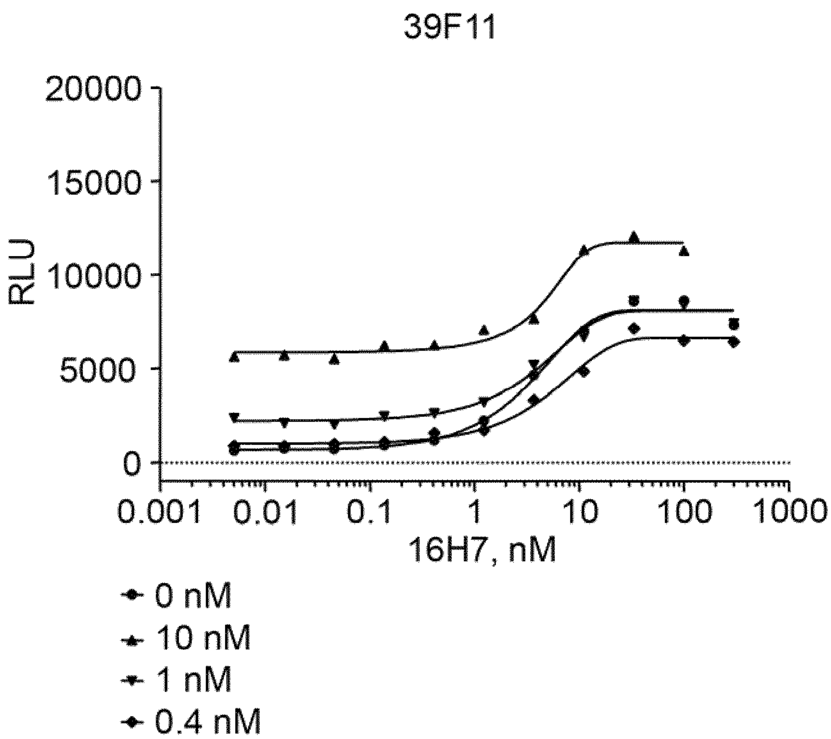


FIG. 35B



HUMAN ANTIGEN BINDING PROTEINS THAT BIND β-KLOTHO, FGF RECEPTORS AND COMPLEXES THEREOF

This application claims the benefit of U.S. Provisional Application No. 61/267,321 filed Dec. 7, 2009 and U.S. Provisional Application No. 61/381,846 filed Sep. 10, 2010, which are incorporated by reference herein.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Nov. 24, 2010, is named A-1519-NP.txt and is 645,894 bytes in size.

FIELD OF THE INVENTION

The present disclosure relates to nucleic acid molecules encoding antigen binding proteins that bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. The present disclosure also provides antigen binding proteins that bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, including antigen binding proteins that induce FGF21-like signaling, as well as pharmaceutical compositions comprising antigen binding proteins that bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, including antigen binding proteins that induce FGF21-like signaling, and methods for treating metabolic disorders using such nucleic acids, polypeptides, or pharmaceutical compositions. Diagnostic methods using the antigen binding proteins are also provided.

BACKGROUND

Fibroblast Growth Factor 21 (FGF21) is a secreted polypeptide that belongs to a subfamily of Fibroblast Growth Factors (FGFs) that includes FGF19, FGF21, and FGF23 (Itoh et al., (2004) *Trend Genet.* 20:563-69). FGF21 is an atypical FGF in that it is heparin independent and functions as a hormone in the regulation of glucose, lipid, and energy metabolism.

It is highly expressed in liver and pancreas and is the only member of the FGF family to be primarily expressed in liver. Transgenic mice overexpressing FGF21 exhibit metabolic phenotypes of slow growth rate, low plasma glucose and triglyceride levels, and an absence of age-associated type 2 diabetes, islet hyperplasia, and obesity. Pharmacological administration of recombinant FGF21 protein in rodent and primate models results in normalized levels of plasma glucose, reduced triglyceride and cholesterol levels, and improved glucose tolerance and insulin sensitivity. In addition, FGF21 reduces body weight and body fat by increasing energy expenditure, physical activity, and metabolic rate. Experimental research provides support for the pharmacological administration of FGF21 for the treatment of type 2 diabetes, obesity, dyslipidemia, and other metabolic conditions or disorders in humans.

FGF21 is a liver derived endocrine hormone that stimulates glucose uptake in adipocytes and lipid homeostasis through the activation of its receptor. Interestingly, in addition to the canonical FGF receptor, the FGF21 receptor also comprises

the membrane associated β-Klotho as an essential cofactor. Activation of the FGF21 receptor leads to multiple effects on a variety of metabolic parameters.

In mammals, FGFs mediate their action via a set of four FGF receptors, FGFR1-4, that in turn are expressed in multiple spliced variants, e.g., FGFR1c, FGFR2c, FGFR3c and FGFR4. Each FGF receptor contains an intracellular tyrosine kinase domain that is activated upon ligand binding, leading to downstream signaling pathways involving MAPKs (Erk1/2), RAFT, AKT1 and STATs. (Kharitonenkov et al., (2008) *BioDrugs* 22:37-44). Several reports suggested that the "c"-reporter splice variants of FGFR1-3 exhibit specific affinity to β-Klotho and could act as endogenous receptor for FGF21 (Kurosu et al., (2007) *J. Biol. Chem.* 282:26687-26695); Ogawa et al., (2007) *Proc. Natl. Acad. Sci. USA* 104:7432-7437); Kharitonenkov et al., (2008) *J. Cell Physiol.* 215:1-7). In the liver, which abundantly expresses both β-Klotho and FGFR4, FGF21 does not induce phosphorylation of MAPK albeit the strong binding of FGF21 to the β-Klotho-FGFR4 complex. In 3T3-L1 cells and white adipose tissue, FGFR1 is by far the most abundant receptor, and it is therefore most likely that FGF21's main functional receptors in this tissue are the β-Klotho/FGFR1c complexes.

The present disclosure provides a human (or humanized) antigen binding protein, such as a monoclonal antibody, that induces FGF21-like signaling, e.g., an agonistic antibody that mimics the function of FGF21. Such an antibody is a molecule with FGF21-like activity and selectivity but with added therapeutically desirable characteristics typical for an antibody such as protein stability, lack of immunogenicity, ease of production and long half-life in vivo.

SUMMARY

An isolated antigen binding protein that induces FGF21-mediated signaling is provided.

Also provided is an isolated antigen binding protein that specifically binds to at least one of: (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; and (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c and FGFR4 wherein the antigen binding protein induces FGF21-mediated signaling.

In one embodiment, the provided antigen binding proteins comprise an amino acid sequence selected from the group consisting of: (a) a light chain CDR3 comprising a sequence selected from the group consisting of: (i) a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the light chain CDR3 sequences of L1-L18, SEQ ID NOs: 180-194; (ii) QVWDX_1X_2SDHVV (SEQ ID NO: 276); (iii) QQX3G$X_4X_5X_6X_7$T (SEQ ID NO: 283); (iv) LQHNSYPLT (SEQ ID NO: 267); (v) MQSLQTPFT (SEQ ID NO: 268); (vi) QQYNNWPPT (SEQ ID NO: 269); (vii) MQSIQLPRT (SEQ ID NO: 270); (viii) QQANDFPIT (SEQ ID NO: 271); (ix) MQALQTPCS (SEQ ID NO: 272); (b) a heavy chain CDR3 sequence comprising a sequence selected from the group consisting of: (i) a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the heavy chain CDR3 sequences of H1-H18, SEQ ID NOs:145-157; (ii) $X_{34}X_{16}X_{17}X_{18}$GX_{19}YYYX_{20}GMDV (SEQ ID NO: 322); (iii) SLIVVX_{21}VY X_{22}LDX_{23} (SEQ ID NO: 326); (iv) IVVVPAAIQSYYYYYGMGV (SEQ ID NO: 311); (v) DPDGDYYYYGMDV (SEQ ID NO: 312); (vi) TYSSGWYVWDYYGMDV (SEQ ID NO: 313); (vii) DRVL-

SYYAMAV (SEQ ID NO: 314); (viii) VRIAGDYY YYYG-MDV (SEQ ID NO: 315); (ix) ENIVVIPAAIFAGWFDP (SEQ ID NO: 316); and (x) DRAAAGLHYYYGMDV (SEQ ID NO: 317); or (c) the light chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b); wherein, X_1 is G, S or N; X_2 is N, S or T; X_3 is C, Y or S; X_4 is G or S; X_5 is A or S; X_6 is P or F; X_7 is L or absent; X_{34} is I, V or S; X_{16} is L or V; X_{17} is L, T or V; X_{18} is L, V, G or T; X_{19} is A, G or absent; X_{20} is Y, C or D; X_{21} is I or M; X_{22} is A or V; and X_{23} is H or Y; and wherein the antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In another embodiment the provided antigen binding proteins comprise either: (a) a light chain CDR1 sequence selected from the group consisting of: (i) a light chain CDR1 that differs by no more than three amino acids additions, substitutions, and/or deletions from a CDR1 sequence of L1-L18, SEQ ID NOs:158-170; (ii) RASQ $X_9X_{10}X_{11}X_{12}X_{13}X_{14}$LA (SEQ ID NO: 304); (iii) GGNNIGSX_{15}SVH (SEQ ID NO: 307); (iv) RSSQSLL$X_{29}X_{30}$NG$X_{31}X_{32}X_{33}$LD (SEQ ID NO: 310); (v) RASQSVNSNLA (SEQ ID NO: 295); (vi) RASQDIRYDLG (SEQ ID NO: 296); (vii) RASQGISIWLA (SEQ ID NO: 297); and (viii) KSSQSLLQSDGKTYLY (SEQ ID NO: 298); (b) a light chain CDR2 sequence selected from the group consisting of: (i) a light chain CDR2 that differs by no more than two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L18, SEQ ID NOs: 171-179; (ii) LGSX_{27}RAS (SEQ ID NO: 290); (iii) GX_8SX_{28}RAT (SEQ ID NO: 294); (iv) AASSLQS (SEQ ID NO: 284); (v) GVSTRAT (SEQ ID NO: 285); (vi) DDSDRPS (SEQ ID NO: 286); (vii) EVSNRFS (SEQ ID NO: 287); (c) a heavy chain CDR1 sequence selected from the group consisting of: (i) a heavy chain CDR1 that differs by no more than two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H18, SEQ ID NOs:121-131; and (ii) NARMGVX_{39} (SEQ ID NO: 352); (iii) X_{40}YGIH (SEQ ID NO: 355); (iv) DLSMH (SEQ ID NO: 345); (v) DAWMS (SEQ ID NO: 346); (vi) TYAMS (SEQ ID NO: 347); (vii) SYFWS (SEQ ID NO: 348); (viii) SYYWS (SEQ ID NO: 131); (ix) SGGYNWS (SEQ ID NO: 349); (d) a heavy chain CDR2 selected from the group consisting of: (i) a heavy sequence that differs by no more than three amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H18, SEQ ID NOs:132-144; (ii) HIFSNDE-KSYSTSLKX_{24} (SEQ ID NO: 333); (iii) X_{251}SGSGVSTX_{26}YADSVKG (SEQ ID NO: 338); (iv) VIWYDGSX_{35}KYYX_{36}DSVKG (SEQ ID NO: 341); (v) X_{371}YX_{38}SGSTX_{41}YNPSLKS (SEQ ID NO: 344); (vi) GFDPEDGETIYAQKFQG (SEQ ID NO: 327); (vii) RIKSK-TDGGTTDYAAPVKG (SEQ ID NO: 328); (viii) RIYTSG-STNYNPSLKS (SEQ ID NO: 329); (ix) RIKSKDG-GTTDYAAPVKG (SEQ ID NO: 330); (x) RIKSKX_{42}DGGTTDYAAPVKG (SEQ ID NO: 483); wherein X_9 is N or S; X_{10} is V or F; X_{11} is D or S; X_{12} is G or S; X_{13} is S, N or T; X_{14} is S or Y; X_{15} is E or Q; X_{29} is Y or H; X_{30} is Y or S; X_{31} is F or Y; X_{32} is T or N; X_{33} is Y or F; X_{27} is N or D; X_8 is A or T; X_{28} is S or F; X_{39} is S or N; X_{24} is S or N; X_{25} is G or A; X_{26} is H, Y or N; X_{35} is D or I; X_{36} is A or G; X_{37} is N or R; X_{38} is Y or T; X_{41} is Y or N; X_{42} is T or absent; (e) the light chain CDR1 of (a) and the light chain CDR2 of (b); (f) the light chain CDR1 of (a) and the heavy chain CDR1 of (c); (g) the light chain CDR1 of (a) and the heavy chain CDR2 of (d); (h) the light chain CDR1 (b) and the heavy chain CDR1 of (c); (i) the heavy chain CDR1 of (c) and the heavy chain CDR2 of (d); (j) the light chain CDR2 of (b) and the heavy chain CDR2 of (d); (k) the light chain CDR1 of (a), the light chain CDR2 of (b), and the heavy chain CDR1 of (c); (l) the light chain CDR2 of (b), the heavy CDR1 of (c), and the heavy chain CDR2 of (d); (m) the light chain CDR1 of (a), the heavy chain CDR1 of (c), and the heavy chain CDR2 of (d); or (n) the light chain CDR1 of (a), the light chain CDR2 of (b), the heavy chain CDR2 of (c), and the heavy chain CDR2 of (d), wherein said antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In yet another embodiment the provided antigen binding proteins comprise either: (a) a light chain variable domain comprising; (i) a light chain CDR1 sequence selected from SEQ ID NOs:158-170; (ii) a light chain CDR2 sequence selected from SEQ ID NOs:171-179; (iii) a light chain CDR3 sequence selected from SEQ ID NOs:180-194; and (b) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence selected from SEQ ID NOs:121-131; (ii) a heavy chain CDR2 sequence selected from SEQ ID NOs: 132-144; and (iii) a heavy chain CDR3 sequence selected from SEQ ID NOs:145-157; or (c) the light chain variable domain of (a) and the heavy chain variable domain of (b), wherein the antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In a further embodiment the provided antigen binding proteins comprise either: (a) a light chain variable domain sequence selected from the group consisting of: (i) amino acids having a sequence at least 80% identical to a light chain variable domain sequence selected from V_L1-V_L18, SEQ ID NOs:48-65; (ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the light chain variable domain sequence of V_L1-V_L18, SEQ ID NOs:48-65; (b) a heavy chain variable domain sequence selected from the group consisting of: (i) a sequence of amino acids that is at least 80% identical to a heavy chain variable domain sequence of V_H1-V_H18 of SEQ ID NOs:66-84; (ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the heavy chain variable domain sequence of V_H1-V_H18, SEQ ID NOs:66-84; or (c) the light chain variable domain of (a) and the heavy chain variable domain of (b); wherein the antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In particular embodiments the provided antigen binding proteins comprise either: (a) a light chain variable domain sequence selected from the group consisting of: V_L1-V_L18 of SEQ ID NOs:48-65; (b) a heavy chain variable domain sequence selected from the group consisting of: V_H1-V_H18 of SEQ ID NOs:66-84; or (c) the light chain variable domain of (a) and the heavy chain variable domain of (b), wherein the antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In other particular embodiments, the provided antigen binding proteins the light chain variable domain and a heavy chain variable domain are selected from the group of combinations consisting of: V_L1V_H1, V_L2V_H2, V_L3V_H3, V_L3V_H4, V_L4V_H5, V_L5V_H6, V_L6V_H7, V_L7V_H8, V_L8V_H8, V_L9V_H9, V_L9V_H10, V_L10V_H11, V_L11V_H11, V_L12V_H12, V_L13V_H13, V_L14V_H14, V_L15V_H15, V_L16V_H16, V_L17V_H17, and V_L18V_H18, wherein the antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In still further embodiments the provided antigen binding proteins further comprise: (a) the light chain constant sequence of SEQ ID NO: 10; (b) the light chain constant sequence of SEQ ID NO:11; (c) the heavy chain constant sequence of SEQ ID NO: 9; or (d) the light chain constant sequence of SEQ ID NO: 10 or SEQ ID NO:11 and the heavy chain constant sequence of SEQ ID NO: 9.

The provided antigen binding proteins can take many forms and can be, for example, a human antibody, a humanized antibody, chimeric antibody, a monoclonal antibody, a polyclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an $F(fab')_2$ fragment, a domain antibody, an IgD antibody, an IgE antibody, an IgM antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, an IgG4 antibody, or an IgG4 antibody having at least one mutation in the hinge region.

In another embodiment, the provided antigen binding proteins when bound to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4: (a) bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, with substantially the same Kd as a reference antibody; (b) induce FGF21-like signaling of 10% or greater than the signaling induced by a wild-type FGF21 standard comprising the mature form of SEQ ID NO:2 as measured in an ELK-luciferase reporter assay; (c) exhibit an EC50 of 10 nM or less of FGF21-like signaling in an assay selected from the group consisting of: (i) a FGFR1c/β-Klotho-mediated in vitro recombinant cell-based assay; and (ii) an in vitro human adipocyte functional assay; (d) exhibit an EC50 of less than 10 nM of agonistic activity on FGFR1c in the presence of β-Klotho in an in vitro recombinant FGFR1c receptor mediated reporter assay; and (e) exhibit an EC50 of greater than 1 μM of agonistic activity on FGFR1c in the absence of β-Klotho in an in vitro recombinant FGFR1c receptor mediated reporter assay; or (f) competes for binding with a reference antibody to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, wherein the reference antibody comprises a combination of light chain and heavy chain variable domain sequences selected from the group consisting of V_L1V_H1, V_L2V_H2, V_L3V_H3, V_L3V_H4, V_L4V_H5, V_L5V_H6, V_L6V_H7, V_L7V_H8, V_L8V_H8, V_L9V_H9, V_L9V_H10, V_L10V_H11, V_L11V_H11, V_L12V_H12, V_L13V_H13, V_L14V_H14, V_L15V_H15, V_L16V_H16, V_L17V_H17, and V_L18V_H18. In other embodiments the provided antigen binding proteins can when bound to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4: (a) lower blood glucose in an animal model; (b) lower serum lipid levels in an animal model; (c) lower insulin levels in an animal model; or (d) two or more of (a) and (b) and (c).

In specific embodiments the provided antigen binding proteins comprise: (a) a heavy chain comprising one of SEQ ID NOs:31, 32, 390-401, 404-405; (b) a light chain comprising one of SEQ ID NO:13, 14, 385-389, 402-403; or (c) a combination comprising a heavy chain of (a) and a light chain of (b).

Also provided are antigen binding proteins that are capable of binding wild type human β-Klotho (SEQ ID NO:7) but which doesn't bind to a chimeric form of β-Klotho wherein the chimeric form of β-Klotho comprises a human β-Klotho framework wherein murine β-Klotho sequences replace the wild type human residues at least one of (a) positions 1-80; (b) positions 303-522; (c) positions 852-1044; and (d) combinations thereof.

In another aspect, the present disclosure provides antigen binding proteins that are capable of binding wild type human β-Klotho (SEQ ID NO:7) at least one of (a) positions 1-80; (b) positions 303-522; (c) positions 852-1044; and (d) combinations thereof.

In still another aspect, the present disclosure provides antigen binding proteins that are capable of competing with an antigen binding protein of claim **8** or **13** for binding to human wild type β-Klotho residues at least one of (a) positions 1-80; (b) positions 303-522; (c) positions 852-1044; and (d) combinations thereof.

Also provided is a pharmaceutical composition comprising one or more antigen binding proteins provided herein, in admixture with a pharmaceutically acceptable carrier thereof.

In a further aspect, also provided are isolated nucleic acid molecules that encode the antigen binding proteins disclosed herein. In some instances, the isolated nucleic acid molecules are operably-linked to a control sequence. In embodiments, such nucleic acids comprise a polynucleotide sequence encoding the light chain variable domain, the heavy chain variable domain, or both, of an antigen binding protein provided herein. In particular embodiments the nucleic acids comprise (a) V_L1-V_L18 (SEQ ID NOs:48-65); (b) V_H1-V_H18 (SEQ ID NOs:66-84); or (c) one or more sequences of (a) and one or more sequences of (b).

In another aspect, also provided are expression vectors and host cells transformed or transfected with the expression vectors that comprise the aforementioned isolated nucleic acid molecules that encode the antigen binding proteins disclosed herein.

In another aspect, also provided are methods of preparing antigen binding proteins that specifically or selectively bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and comprises the step of preparing the antigen binding protein from a host cell that secretes the antigen binding protein.

Other embodiments provide a method of preventing or treating a condition in a subject in need of such treatment comprising administering a therapeutically effective amount of a pharmaceutical composition provided herein to a subject, wherein the condition is treatable by lowering blood glucose, insulin or serum lipid levels. In embodiments, the condition is type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease or metabolic syndrome.

These and other aspects are described in greater detail herein. Each of the aspects provided can encompass various embodiments provided herein. It is therefore anticipated that each of the embodiments involving one element or combinations of elements can be included in each aspect described, and all such combinations of the above aspects and embodiments are expressly considered. Other features, objects, and advantages of the disclosed antigen binding proteins and associated methods and compositions are apparent in the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1A-1B** is an alignment showing the sequence homology between human FGFR1c (GenBank™ Accession No P11362; SEQ ID NO: 356) and murine FGFR1c (GenBank™ Accession No NP_034336; SEQ ID NO: 357); various features are highlighted, including the signal peptide, transmembrane sequence, heparin binding region, and a consensus sequence (SEQ ID NO: 358) is provided.

FIG. **2***a*-**2***c* is an alignment showing the sequence homology between human β-Klotho (GenBank™ Accession No NP_783864; SEQ ID NO: 359) and murine β-Klotho (GenBank™ Accession No NP_112457; SEQ ID NO: 360); various features are highlighted, including the transmembrane sequence and two glycosyl hydrolase domains, and a consensus sequence (SEQ ID NO: 361) is provided.

FIGS. **3**A-**3**F are a flow cytometry profile of cells stained with FGF21-Alexa 647 that were used as an immunogen to generate antigen binding proteins; the figure shows the expression level of an FGF21R (a complex comprising FGFR1c and β-Klotho) and binding to FGF21.

FIG. **4** is a sequence (SEQ ID NO: 362) showing an Fc fusion protein that was used as an immunogen to generate antigen binding proteins; the immunogen comprises the extracellular domain (ECD) of human FGFR1c fused to an IgG1 Fc via a Gly_5 linker (SEQ ID NO: 379); the FGFR1c component is in capitals, the linker is italic and underlined and the Fc is in lower case letters.

FIG. **5** is a sequence (SEQ ID NO: 363) showing an Fc fusion protein that was used as an immunogen to generate antigen binding proteins; the immunogen comprises the extracellular domain (ECD) of human β-Klotho fused to an IgG1 Fc via a Gly_5 linker (SEQ ID NO: 379); the β-Klotho component is in capitals, the linker is italic and underlined and the Fc is in lower case letters.

FIG. **6** is a SDS PAGE gel showing the level of purity achieved from preparations of a soluble FGF21 receptor complex comprising FGFR1c ECD-Fc and β-Klotho ECD-Fc, which was employed as an immunogen to generate antigen binding proteins.

FIGS. **7**A-D are a series of plots generated from an ELK-luciferase reporter assay as described herein performed on recombinant CHO clone 2E10, demonstrating the ability of some of the antigen binding proteins to induce FGF21-like signaling in recombinant CHO cells expressing a FGF21 receptor complex comprising FGFR1c and β-Klotho.

FIGS. **8**A-**8**C are a series of plots generated from an ERK 1/2 phosphorylation assay as described herein, demonstrating the ability of some of the antigen binding proteins to induce FGF21-like signaling in rat L6 cells. The X-axis is the concentrations of the antigen binding proteins and the Y-axis is the percentage of phosphorylated ERK 1/2 of total ERK 1/2.

FIGS. **9**A-**9**D are a series of plots generated from an ERK 1/2 phosphorylation assay as described herein, demonstrating that antigen binding protein-mediated FGF21-like signaling in L6 cells is FGFR1c/β-Klotho specific.

FIGS. **10**A-**10**D are a series of plots generated from an ERK phosphorylation assay as described herein, demonstrating that some antigen binding proteins are able to induce FGF21-like signaling in human adipocyte cells.

FIGS. **11**A-**11**C are a series of binding sensorgrams (response units vs time) demonstrating that some of the antigen binding proteins that induce FGF21-mediated signaling bind to human β-Klotho at two different but partially overlapping binding sites represented by 24H11 (Group A) and 17D8 (Group B), while antigen binding proteins that do not induce FGF21-mediated signaling (2G10, 1A2) do not bind to these sites.

FIGS. **11**B-**11**F are a series of binding sensorgrams (response units vs time) demonstrating a third binding site on human β-Klotho that was identified for Group C antigen binding proteins represented by 39F7.

FIG. **11**G is a table summarizing epitope binning.

FIG. **12** is a series of binding sensorgrams (response units vs time) demonstrating that some of the antigen binding proteins (12E4, 24H11, 17C3, 18B11) that induce FGF21-mediated signaling interfere with β-Klotho binding to FGF21, while other antigen binding proteins (21H2, 17D8, 18G1) do not.

FIGS. **13**A-**13**F are an alignment of the variable regions of some of the antigen binding proteins that were generated: the framework and CDR regions are identified. FIG. **13** discloses SEQ ID NOS: 364, 59, 365, 60, 366, 61, 367, 62, 368, 57, 369, 55, 51-52, 56. 56, 53-54, 63-65, 370, 58, 371, 50, 50, 49, 48, 372 78, 373, 66-69, 79, 374, 76, 81, 375, 70, 73, 73, 71-72, 376, 83, 82, 84, 377, 80, 378, 75 and 74, respectively, in order of appearance.

FIG. **14** is a diagram graphically depicting the study design for a 68 days study performed in obese cynomolgus monkeys.

FIG. **15** is a plot depicting the effects of vehicle and 16H7 on AM meal food intake of the obese cynomolgus monkeys studied.

FIGS. **16**A-**16**B are two plots depicting the effects of vehicle and 16H7 on fruit intake and PM food intake of the obese cynomolgus monkeys studied.

FIGS. **17**A-**17**B are a plot depicting the effects of vehicle and 16H7 on body weight of the obese cynomolgus monkeys studied.

FIGS. **18**A-**18**B are a plot showing the effects of vehicle and 16H7 on body mass index (BMI) of the obese cynomolgus monkeys studied.

FIGS. **19**A-**19**B are a plot showing the effects of vehicle on abdominal circumference (AC) of the obese cynomolgus monkeys studied.

FIGS. **20**A-**20**B are a plot showing the effects of vehicle and 16H7 on skin fold thickness (SFT) of the obese cynomolgus monkeys studied.

FIGS. **21**A-**21**D are a plot showing the effects of vehicle and 16H7 on glucose levels during glucose tolerance tests of the obese cynomolgus monkeys studied.

FIGS. **22**A-**22**D are a plot showing the effects of vehicle and 16H7 on plasma insulin levels during glucose tolerance tests of the obese cynomolgus monkeys studied.

FIGS. **23**A-**23**B are a plot showing the effects of vehicle and 16H7 on fasting plasma glucose levels of the obese cynomolgus monkeys studied.

FIGS. **24**A-**24**B are a plot showing the effects of vehicle and 16H7 on fasting plasma insulin levels of the obese cynomolgus monkeys studied.

FIGS. **25**A-**25**B are a plot showing the effects of vehicle and 16H7 on fed plasma glucose levels of the obese cynomolgus monkeys studied.

FIGS. **26**A-**26**B are a plot showing the effects of vehicle and 16H7 on fed plasma insulin levels of the obese cynomolgus monkeys studied.

FIGS. **27**A-**27**B are a plot showing the effects of vehicle and 16H7 on fasting plasma triglyceride levels of the obese cynomolgus monkeys studied.

FIGS. **28**A-**28**B are a plot showing the effects of vehicle and 16H7 on fed plasma triglyceride levels of the obese cynomolgus monkeys studied.

FIG. **29** is a schematic depicting human-mouse β-Klotho chimeras that were constructed and used to studying the binding of antigen binding proteins.

FIG. **30** is a schematic depicting the human-mouse β-Klotho chimeras that were constructed and also includes qualitative binding data for FGF21, 16H7, 37D3 and 39F7.

FIG. **31**A-C is a series of plots depicting binding data for eight of the 16H7 and 22H5 variants that were constructed, as well as for 22H5 and 16H7.

FIGS. **32**A-C is a series of plots depicting the results of ELISA assays that were used to demonstrate that several of the 22H5 and 16H7 variants have binding ability.

FIG. **33** is a bar graph comparing off-rates for several 22H5 and 17H7 variants that were generated.

FIGS. **34**A-**34**B are, two plots that depict binding curves for 39F11 when titrated with FGF21 and for FGF21 when titrated with 39F11; the plots demonstrate an additive effect.

FIGS. **35**A-**35**B are two plots that depict binding curves for 16H7 when titrated with 39F11 and 39F11 when it is titrated with 16H7; the plots demonstrate an additive effect.

DETAILED DESCRIPTION

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Unless otherwise defined herein, scientific and technical terms used in connection with the present application shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present application are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001), Ausubel et al., Current Protocols in Molecular Biology, Greene Publishing Associates (1992), and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990), which are incorporated herein by reference. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The terminology used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

It should be understood that the instant disclosure is not limited to the particular methodology, protocols, and reagents, etc., described herein and as such can vary. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present disclosure.

Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about." The term "about" when used in connection with percentages can mean±5%, e.g., 1%, 2%, 3%, or 4%.

I. Definitions

As used herein, the terms "a" and "an" mean "one or more" unless specifically stated otherwise.

An "antigen binding protein" is a protein comprising a portion that binds to an antigen or target and, optionally, a scaffold or framework portion that allows the antigen binding portion to adopt a conformation that promotes binding of the antigen binding protein to the antigen. Examples of antigen binding proteins include a human antibody, a humanized antibody; a chimeric antibody; a recombinant antibody; a single chain antibody; a diabody; a triabody; a tetrabody; a Fab fragment; a $F(ab')_2$ fragment; an IgD antibody; an IgE antibody; an IgM antibody; an IgG1 antibody; an IgG2 antibody; an IgG3 antibody; or an IgG4 antibody, and fragments thereof. The antigen binding protein can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. See, e.g., Korndorfer et al., 2003, *Proteins: Structure, Function, and Bioinformatics,* 53(1):121-129 (2003); Roque et al., *Biotechnol. Prog.* 20:639-654 (2004). In addition, peptide antibody mimetics ("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronectin components as a scaffold.

An antigen binding protein can have, for example, the structure of a naturally occurring immunoglobulin. An "immunoglobulin" is a tetrameric molecule. In a naturally occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2^{nd} ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

Naturally occurring immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain can be done in accordance with the definitions of Kabat et al. in Sequences of Proteins of Immunological Interest, 5^{th} Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. As desired, the CDRs can also be redefined according an alternative nomenclature scheme, such as that of Chothia (see Chothia & Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia et al., 1989, *Nature* 342:878-883 or Honegger & Pluckthun, 2001, *J. Mol. Biol.* 309:657-670).

In the context of the instant disclosure an antigen binding protein is said to "specifically bind" or "selectively bind" its target antigen when the dissociation constant (K_D) is $\leq 10^{-8}$ M. The antibody specifically binds antigen with "high affinity" when the K_D is $\leq 5\times10^{-9}$ M, and with "very high affinity" when the K_D is $\leq 5\times10^{-10}$ M. In one embodiment, the antibodies will bind to FGFR1c, β-Klotho, both FGFR1c and β-Klotho or a complex comprising FGFR1c and β-Klotho, including human FGFR1c, human β-Klotho or both human FGFR1c and human β-Klotho, with a K_D of between about 10^{-7} M and 10^{-12} M, and in yet another embodiment the antibodies will bind with a $K_D \leq 5\times10^{-9}$.

An "antibody" refers to an intact immunoglobulin or to an antigen binding portion thereof that competes with the intact antibody for specific binding, unless otherwise specified. Antigen binding portions can be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen binding portions include, inter alia, Fab, Fab', $F(ab')_2$, Fv, domain antibodies (dAbs), fragments including complementarity determining regions (CDRs), single-chain antibodies (scFv), chimeric antibodies, diabodies, triabodies, tetrabodies, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

A Fab fragment is a monovalent fragment having the V_L, V_H, C_L and C_H1 domains; a $F(ab')_2$ fragment is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment has the V_H and C_H1 domains; an Fv fragment has the V_L and V_H domains of a single arm of an antibody; and a dAb fragment has a V_H domain, a V_L domain, or an antigen-binding fragment of a V_H or V_L domain (U.S. Pat. Nos. 6,846,634, 6,696,245, U.S. application Pub. Ser. Nos. 05/0202512, 04/0202995, 04/0038291, 04/0009507, 03/0039958, Ward et al., Nature 341:544-546 (1989)).

A single-chain antibody (scFv) is an antibody in which a V_L and a V_H region are joined via a linker (e.g., a synthetic sequence of amino acid residues) to form a continuous protein chain wherein the linker is long enough to allow the protein chain to fold back on itself and form a monovalent antigen binding site (see, e.g., Bird et al., *Science* 242:423-26 (1988) and Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-83 (1988)). Diabodies are bivalent antibodies comprising two polypeptide chains, wherein each polypeptide chain comprises V_H and V_L domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (see, e.g., Holliger et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:6444-48 (1993), and Poljak et al., *Structure* 2:1121-23 (1994)). If the two polypeptide chains of a diabody are identical, then a diabody resulting from their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen binding sites. Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different.

Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody can be identified using the system described by Kabat et al. in Sequences of Proteins of Immunological Interest, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991 As desired, the CDRs can also be redefined according an alternative nomenclature scheme, such as that of Chothia (see Chothia & Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia et al., 1989, *Nature* 342:878-883 or Honegger & Pluckthun, 2001, *J. Mol. Biol.* 309:657-670. One or more CDRs can be incorporated into a molecule either covalently or noncovalently to make it an antigen binding protein. An antigen binding protein can incorporate the CDR(s) as part of a larger polypeptide chain, can covalently link the CDR(s) to another polypeptide chain, or can incorporate the CDR(s) noncovalently. The CDRs permit the antigen binding protein to specifically bind to a particular antigen of interest.

An antigen binding protein can have one or more binding sites. If there is more than one binding site, the binding sites can be identical to one another or can be different. For example, a naturally occurring human immunoglobulin typically has two identical binding sites, while a "bispecific" or "bifunctional" antibody has two different binding sites.

The term "human antibody" includes all antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences. In one embodiment, all of the variable and constant domains are derived from human immunoglobulin sequences (a fully human antibody). These antibodies can be prepared in a variety of ways, examples of which are described below, including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes, such as a mouse derived from a Xenomouse®, UltiMab™, or Velocimmune® system. Phage-based approaches can also be employed.

A humanized antibody has a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-human species antibody are mutated to produce the humanized antibody. In another embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies can be found in U.S. Pat. Nos. 6,054,297, 5,886,152 and 5,877,293.

The term "chimeric antibody" refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In one embodiment, one or more of the CDRs are derived from a human antibody that binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In another embodiment, all of the CDRs are derived from a human antibody that binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In another embodiment, the CDRs from more than one human antibody that binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 are mixed and matched in a chimeric antibody. For instance, a chimeric antibody can comprise a CDR1 from the light chain of a first human antibody that binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, a CDR2 and a CDR3 from the light chain of a second human antibody that binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, and the CDRs from the heavy chain from a third antibody that binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Further, the framework regions can be derived from one of the same antibodies that bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, from one or more different antibodies, such as a human antibody, or from a humanized antibody. In one example of a chimeric antibody, a portion of the heavy and/or light chain is identical with, homologous to, or derived from an antibody from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with, homologous to, or derived from an antibody or antibodies from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies that exhibit the desired biological activity (e.g., the ability to specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4).

The term "light chain" includes a full-length light chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length light chain includes a variable region domain, V_L, and a constant region domain, C_L. The variable region domain of the light chain is at the amino-terminus of the polypeptide. Light chains include kappa ("κ") chains and lambda ("λ") chains.

The term "heavy chain" includes a full-length heavy chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length heavy chain includes a variable region domain, V_H, and three constant region domains, C_H1, C_H2, and C_H3. The V_H domain is at the amino-terminus of the polypeptide, and the C_H domains are at the carboxyl-terminus, with the C_H3 being closest to the carboxy-terminus of the polypeptide. Heavy chains can be of any isotype, including IgG (including IgG1, IgG2, IgG3 and IgG4 subtypes), IgA (including IgA1 and IgA2 subtypes), IgM and IgE.

The term "immunologically functional fragment" (or simply "fragment") of an antigen binding protein, e.g., an antibody or immunoglobulin chain (heavy or light chain), as used herein, is an antigen binding protein comprising a portion (regardless of how that portion is obtained or synthesized) of an antibody that lacks at least some of the amino acids present in a full-length chain but which is capable of specifically binding to an antigen. Such fragments are biologically active in that they bind specifically to the target antigen and can compete with other antigen binding proteins, including intact antibodies, for specific binding to a given epitope. In one aspect, such a fragment will retain at least one CDR present in the full-length light or heavy chain, and in some embodiments will comprise a single heavy chain and/or light chain or portion thereof. These biologically active fragments can be produced by recombinant DNA techniques, or can be produced by enzymatic or chemical cleavage of antigen binding proteins, including intact antibodies. Immunologically functional immunoglobulin fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv, domain antibodies and single-chain antibodies, and can be derived from any mammalian source, including but not limited to human, mouse, rat, camelid or rabbit. It is contemplated further that a functional portion of the antigen binding proteins disclosed herein, for example, one or more CDRs, could be covalently bound to a second protein or to a small molecule to create a therapeutic agent directed to a particular target in the body, possessing bifunctional therapeutic properties, or having a prolonged serum half-life.

An "Fc" region contains two heavy chain fragments comprising the C_H2 and C_H3 domains of an antibody. The two heavy chain fragments are held together by two or more disulfide bonds and by hydrophobic interactions of the C_H3 domains.

An "Fab' fragment" contains one light chain and a portion of one heavy chain that contains the V_H domain and the C_H1 domain and also the region between the C_H1 and C_H2 domains, such that an interchain disulfide bond can be formed between the two heavy chains of two Fab' fragments to form an $F(ab')_2$ molecule.

An "$F(ab')_2$ fragment" contains two light chains and two heavy chains containing a portion of the constant region between the C_H1 and C_H2 domains, such that an interchain disulfide bond is formed between the two heavy chains. A $F(ab')_2$ fragment thus is composed of two Fab' fragments that are held together by a disulfide bond between the two heavy chains.

The "Fv region" comprises the variable regions from both the heavy and light chains, but lacks the constant regions.

A "domain antibody" is an immunologically functional immunoglobulin fragment containing only the variable region of a heavy chain or the variable region of a light chain. In some instances, two or more V_H regions are covalently joined with a peptide linker to create a bivalent domain antibody. The two V_H regions of a bivalent domain antibody can target the same or different antigens.

A "hemibody" is an immunologically functional immunoglobulin construct comprising a complete heavy chain, a complete light chain and a second heavy chain Fc region paired with the Fc region of the complete heavy chain. A linker can, but need not, be employed to join the heavy chain Fc region and the second heavy chain Fc region. In particular embodiments a hemibody is a monovalent form of an antigen binding protein disclosed herein. In other embodiments, pairs of charged residues can be employed to associate one Fc region with the second Fc region. The second heavy chain Fc region can comprise, for example, SEQ ID NO:441 and can be joined to the light chain via a linker (e.g., SEQ ID NO:440) An exemplary hemibody heavy chain comprises the sequence SEQ ID NO:453.

A "bivalent antigen binding protein" or "bivalent antibody" comprises two antigen binding sites. In some instances, the two binding sites have the same antigen specificities. Bivalent antigen binding proteins and bivalent antibodies can be bispecific, as described herein.

A multispecific antigen binding protein" or "multispecific antibody" is one that targets more than one antigen or epitope.

A "bispecific," "dual-specific" or "bifunctional" antigen binding protein or antibody is a hybrid antigen binding protein or antibody, respectively, having two different antigen binding sites. Bispecific antigen binding proteins and antibodies are a species of multispecific antigen binding protein or multispecific antibody and can be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai and Lachmann, 1990, *Clin. Exp. Immunol.* 79:315-321; Kostelny et al., 1992, *J. Immunol.* 148:1547-1553. The two binding sites of a bispecific antigen binding protein or antibody will bind to two different epitopes, which can reside on the same or different protein targets.

The terms "FGF21-like signaling" and "induces FGF21-like signaling," when applied to an antigen binding protein of the present disclosure, means that the antigen binding protein mimics, or modulates, an in vivo biological effect induced by the binding of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and induces a biological response that otherwise would result from FGF21 binding to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in vivo. In assessing the binding and specificity of an antigen binding protein, e.g., an antibody or immunologically functional fragment thereof, an antibody or fragment is deemed to induce a biological response when the response is equal to or greater than 5%, and preferably equal to or greater than 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%, of the activity of a wild type FGF21 standard comprising the mature form of SEQ ID NO:2 (i.e., the mature form of the human FGF21 sequence) and has the following properties: exhibiting an efficacy level of equal to or more than 5% of an FGF21 standard, with an EC50 of equal to or less than 100 nM, e.g., 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM or 10 nM in (1) the recombinant FGF21 receptor mediated luciferase-reporter cell assay of Example 5; (2) ERK-phosphorylation in the recombinant FGF21 receptor mediated cell assay of Example 5; and (3) ERK-phosphorylation in human adipocytes as described in Example 7. The "potency" of an antigen binding protein is defined as exhibiting an EC50 of equal to or less than 100 nM, e.g., 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM and preferably less than 10 nM of the antigen binding protein in the following assays: (1) the recombinant FGF21 receptor mediated luciferase-reporter cell assay of Example 5; (2) the ERK-phosphorylation in the recombinant FGF21 receptor mediated cell assay of Example 5; and (3) ERK-phosphorylation in human adipocytes as described in Example 7.

It is noted that not all of the antigen binding proteins of the present disclosure induce FGF21-mediated signaling, nor is this property desirable in all circumstances. Nevertheless, antigen binding proteins that do not induce FGF21-mediated signaling form aspects of the present disclosure and may be useful as diagnostic reagents or other applications.

As used herein, the term "FGF21R" means a multimeric receptor complex that FGF21 is known or suspected to form in vivo. In various embodiments, FGF21R comprises (i) an FGFR, e.g., FGFR1c, FGFR2c, FGFR3c or FGFR4, and (ii) β-Klotho.

The term "polynucleotide" or "nucleic acid" includes both single-stranded and double-stranded nucleotide polymers. The nucleotides comprising the polynucleotide can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. Said modifications include base modifications such as bromouridine and inosine derivatives, ribose modifications such as 2',3'-dideoxyribose, and internucleotide linkage modifications such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate and phosphoroamidate.

The term "oligonucleotide" means a polynucleotide comprising 200 or fewer nucleotides. In some embodiments, oligonucleotides are 10 to 60 bases in length. In other embodiments, oligonucleotides are 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 nucleotides in length. Oligonucleotides can be single stranded or double stranded, e.g., for use in the construction of a mutant gene. Oligonucleotides can be sense or antisense oligonucleotides. An oligonucleotide can include a label, including a radiolabel, a fluorescent label, a hapten or an antigenic label, for detection assays. Oligonucleotides can be used, for example, as PCR primers, cloning primers or hybridization probes.

An "isolated nucleic acid molecule" means a DNA or RNA of genomic, mRNA, cDNA, or synthetic origin or some combination thereof which is not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature, or is linked to a polynucleotide to which it is not linked in nature. For purposes of this disclosure, it is understood that "a nucleic acid molecule comprising" a particular nucleotide sequence does not encompass intact chromosomes. Isolated nucleic acid molecules "comprising" specified nucleic acid sequences can include, in addition to the specified sequences, coding sequences for up to ten or even up to twenty other proteins or portions thereof, or can include operably linked regulatory sequences that control expression of the coding region of the recited nucleic acid sequences, and/or can include vector sequences.

Unless specified otherwise, the left-hand end of any single-stranded polynucleotide sequence discussed herein is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA transcript that are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences;" sequence regions on the DNA strand having the same sequence as the RNA transcript that are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences."

The term "control sequence" refers to a polynucleotide sequence that can affect the expression and processing of coding sequences to which it is ligated. The nature of such control sequences can depend upon the host organism. In particular embodiments, control sequences for prokaryotes can include a promoter, a ribosomal binding site, and a transcription termination sequence. For example, control sequences for eukaryotes can include promoters comprising one or a plurality of recognition sites for transcription factors, transcription enhancer sequences, and transcription termination sequence. "Control sequences" can include leader sequences and/or fusion partner sequences.

The term "vector" means any molecule or entity (e.g., nucleic acid, plasmid, bacteriophage or virus) used to transfer protein coding information into a host cell.

The term "expression vector" or "expression construct" refers to a vector that is suitable for transformation of a host cell and contains nucleic acid sequences that direct and/or control (in conjunction with the host cell) expression of one or more heterologous coding regions operatively linked thereto. An expression construct can include, but is not limited to, sequences that affect or control transcription, translation, and, if introns are present, affect RNA splicing of a coding region operably linked thereto.

As used herein, "operably linked" means that the components to which the term is applied are in a relationship that allows them to carry out their inherent functions under suitable conditions. For example, a control sequence in a vector that is "operably linked" to a protein coding sequence is ligated thereto so that expression of the protein coding sequence is achieved under conditions compatible with the transcriptional activity of the control sequences.

The term "host cell" means a cell that has been transformed, or is capable of being transformed, with a nucleic acid sequence and thereby expresses a gene of interest. The term includes the progeny of the parent cell, whether or not the progeny is identical in morphology or in genetic make-up to the original parent cell, so long as the gene of interest is present.

The term "transduction" means the transfer of genes from one bacterium to another, usually by bacteriophage. "Transduction" also refers to the acquisition and transfer of eukaryotic cellular sequences by replication-defective retroviruses.

The term "transfection" means the uptake of foreign or exogenous DNA by a cell, and a cell has been "transfected" when the exogenous DNA has been introduced inside the cell membrane. A number of transfection techniques are well known in the art and are disclosed herein. See, e.g., Graham et al., (1973) *Virology* 52:456; Sambrook et al., (2001) Molecular Cloning: A Laboratory Manual, supra; Davis et al., (1986) *Basic Methods in Molecular Biology*, Elsevier; Chu et al., (1981) *Gene* 13:197. Such techniques can be used to introduce one or more exogenous DNA moieties into suitable host cells.

The term "transformation" refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to contain new DNA or RNA. For example, a cell is transformed where it is genetically modified from its native state by introducing new genetic material via transfection, transduction, or other techniques. Following transfection or transduction, the transforming DNA can recombine with that of the cell by physically integrating into a chromosome of the cell, or can be maintained transiently as an episomal element without being replicated, or can replicate independently as a plasmid. A cell is considered to have been "stably transformed" when the transforming DNA is replicated with the division of the cell.

The terms "polypeptide" or "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms also apply to amino acid polymers in which one or more amino acid residues is an analog or mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers. The terms can also encompass amino acid polymers that have been modified, e.g., by the addition of carbohydrate residues to form glycoproteins, or phosphorylated. Polypeptides and proteins can be produced by a naturally-occurring and non-recombinant cell, or polypeptides and proteins can be produced by a genetically-engineered or recombinant cell. Polypeptides and proteins can comprise molecules having the amino acid sequence of a native protein, or molecules having deletions from, additions to, and/or substitutions of one or more amino acids of the native sequence. The terms "polypeptide" and "protein" encompass antigen binding proteins that specifically or selectively bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, or sequences that have deletions from, additions to, and/or substitutions of one or more amino acids of an antigen binding protein that specifically or selectively binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. The term "polypeptide fragment" refers to a polypeptide that has an amino-terminal deletion, a carboxyl-terminal deletion, and/or an internal deletion as compared with the full-length protein. Such fragments can also contain modified amino acids as compared with the full-length protein. In certain embodiments, fragments are about five to 500 amino acids long. For example, fragments can be at least 5, 6, 8, 10, 14, 20, 50, 70, 100, 110, 150, 200, 250, 300, 350, 400, or 450 amino acids long. Useful polypeptide fragments include immunologically functional fragments of antibodies, including binding domains. In the case of an antigen binding protein that binds to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, useful fragments include but are not limited to a CDR region, a variable domain of a heavy or light chain, a portion of an antibody chain or just its variable region including two CDRs, and the like.

The term "isolated protein" referred means that a subject protein (1) is free of at least some other proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (5) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (6) does not occur in nature. Typically, an "isolated protein" constitutes at least about 5%, at least about 10%, at least about 25%, or at least about 50% of a given sample. Genomic DNA, cDNA, mRNA or other RNA, of synthetic origin, or any combination thereof can encode such an isolated protein. Preferably, the isolated protein is substantially free from proteins or polypeptides or other contaminants that are found in its natural environment that would interfere with its therapeutic, diagnostic, prophylactic, research or other use.

A "variant" of a polypeptide (e.g., an antigen binding protein, or an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Variants include fusion proteins.

A "derivative" of a polypeptide is a polypeptide (e.g., an antigen binding protein, or an antibody) that has been chemically modified in some manner distinct from insertion, deletion, or substitution variants, e.g., by conjugation to another chemical moiety.

The term "naturally occurring" as used throughout the specification in connection with biological materials such as polypeptides, nucleic acids, host cells, and the like, refers to materials which are found in nature.

"Antigen binding region" means a protein, or a portion of a protein, that specifically binds a specified antigen, e.g., FGFR1c, β-Klotho or both FGFR1c and β-Klotho. For example, that portion of an antigen binding protein that contains the amino acid residues that interact with an antigen and confer on the antigen binding protein its specificity and affinity for the antigen is referred to as "antigen binding region." An antigen binding region typically includes one or more "complementary binding regions" ("CDRs"). Certain antigen binding regions also include one or more "framework" regions. A "CDR" is an amino acid sequence that contributes to antigen binding specificity and affinity. "Framework" regions can aid in maintaining the proper conformation of the CDRs to promote binding between the antigen binding region and an antigen.

In certain aspects, recombinant antigen binding proteins that bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, are provided. In this context, a "recombinant protein" is a protein made using recombinant techniques, i.e., through the expression of a recombinant nucleic acid as described herein. Methods and techniques for the production of recombinant proteins are well known in the art.

The term "compete" when used in the context of antigen binding proteins (e.g., neutralizing antigen binding proteins, neutralizing antibodies, agonistic antigen binding proteins, agonistic antibodies and binding proteins that bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4) that compete for the same epitope or binding site on a target means competition between antigen binding proteins as determined by an assay in which the antigen binding protein (e.g., antibody or immunologically functional fragment thereof) under study prevents or inhibits the specific binding of a reference molecule (e.g., a reference ligand, or reference antigen binding protein, such as a reference antibody) to a common antigen (e.g., FGFR1c, FGFR2c, FGFR3c, FGFR4, β-Klotho or a fragment thereof). Numerous types of competitive binding assays can be used to determine if a test molecule competes with a reference molecule for binding. Examples of assays that can be employed include solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see, e.g., Stahli et al., (1983) *Methods in Enzymology* 9:242-253); solid phase direct biotin-avidin EIA (see, e.g., Kirkland et al., (1986) *J. Immunol.* 137:3614-3619) solid phase direct labeled assay, solid phase direct labeled sandwich assay (see, e.g., Harlow and Lane, (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Press); solid phase direct label RIA using 1-125 label (see, e.g., Morel et al., (1988) *Molec. Immunol.* 25:7-15); solid phase direct biotin-avidin EIA (see, e.g., Cheung, et al., (1990) *Virology* 176:546-552); and direct labeled RIA (Moldenhauer et al., (1990) *Scand. J. Immunol.* 32:77-82). Typically, such an assay involves the use of a purified antigen bound to a solid surface or cells bearing either of an unlabelled test antigen binding protein or a labeled reference antigen binding protein. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antigen binding protein. Usually the test antigen binding protein is present in excess. Antigen binding proteins identified by competition assay (competing antigen binding proteins) include antigen binding proteins binding to the same epitope as the reference antigen binding proteins and antigen binding proteins binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antigen binding protein for steric hindrance to occur. Additional details regarding methods for determining competitive binding are provided in the examples herein. Usually, when a competing antigen binding protein is present in excess, it will inhibit specific binding of a reference antigen binding protein to a common antigen by at least 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75%. In some instance, binding is inhibited by at least 80%, 85%, 90%, 95%, or 97% or more.

The term "antigen" refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antigen binding protein (including, e.g., an antibody or immunological functional fragment thereof), and may also be capable of being used in an animal to produce antibodies capable of binding to that antigen. An antigen can possess one or more epitopes that are capable of interacting with different antigen binding proteins, e.g., antibodies.

The term "epitope" means the amino acids of a target molecule that are contacted by an antigen binding protein (for example, an antibody) when the antigen binding protein is bound to the target molecule. The term includes any subset of the complete list of amino acids of the target molecule that are contacted when an antigen binding protein, such as an antibody, is bound to the target molecule. An epitope can be contiguous or non-contiguous (e.g., (i) in a single-chain polypeptide, amino acid residues that are not contiguous to one another in the polypeptide sequence but that within in context of the target molecule are bound by the antigen binding protein, or (ii) in a multimeric receptor comprising two or more individual components, e.g., (i) FGFR1c, FGFR2c, FGFR3c or FGFR4, and (ii) β-Klotho, amino acid residues that are present on one or more of the individual components, but which are still bound by the antigen binding protein). In certain embodiments, epitopes can be mimetic in that they comprise a three dimensional structure that is similar to an antigenic epitope used to generate the antigen binding protein, yet comprise none or only some of the amino acid residues found in that epitope used to generate the antigen binding protein. Most often, epitopes reside on proteins, but in some instances can reside on other kinds of molecules, such as nucleic acids. Epitope determinants can include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and can have specific three dimensional structural characteristics, and/or specific charge characteristics. Generally, antigen binding proteins specific for a particular target molecule will preferentially recognize an epitope on the target molecule in a complex mixture of proteins and/or macromolecules.

The term "identity" refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined by aligning and comparing the sequences. "Percent identity" means the percent of identical residues between the amino acids or nucleotides in the compared molecules and is calculated based on the size of the smallest of the molecules being compared. For these calculations, gaps in alignments (if any) must be addressed by a particular mathematical model or computer program (i.e., an "algorithm"). Methods that can be used to calculate the identity of the aligned nucleic acids or polypeptides include those described in *Computational Molecular Biology*, (Lesk, A. M., ed.), (1988) New York: Oxford University Press; Biocomputing Informatics and Genome Projects, (Smith, D. W., ed.), 1993, New York: Academic Press; Computer Analysis of Sequence Data, Part I, (Griffin, A. M., and Griffin, H. G., eds.), 1994, New Jersey: Humana Press; von Heinje, G., (1987) Sequence Analysis in Molecular Biology, New York: Academic Press; Sequence Analysis Primer, (Gribskov, M. and Devereux, J., eds.), 1991, New York: M. Stockton Press; and Carillo et al., (1988) *SIAM J. Applied Math.* 48:1073.

In calculating percent identity, the sequences being compared are aligned in a way that gives the largest match between the sequences. The computer program used to determine percent identity is the GCG program package, which includes GAP (Devereux et al., (1984) *Nucl. Acid Res.* 12:387; Genetics Computer Group, University of Wisconsin, Madison, Wis.). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the "matched span", as determined by the algorithm). A gap opening penalty (which is calculated as 3× the average diagonal, wherein the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (see, Dayhoff et al., (1978) *Atlas of Protein Sequence and Structure* 5:345-352 for the PAM 250 comparison matrix; Henikoff et al., (1992) *Proc. Natl. Acad. Sci. U.S.A.* 89:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm.

Recommended parameters for determining percent identity for polypeptides or nucleotide sequences using the GAP program are the following:

Algorithm: Needleman et al., 1970, *J. Mol. Biol.* 48:443-453;

Comparison matrix: BLOSUM 62 from Henikoff et al., 1992, supra;

Gap Penalty: 12 (but with no penalty for end gaps)

Gap Length Penalty: 4

Threshold of Similarity: 0

Certain alignment schemes for aligning two amino acid sequences can result in matching of only a short region of the two sequences, and this small aligned region can have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method (e.g., the GAP program) can be adjusted if so desired to result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

As used herein, "substantially pure" means that the described species of molecule is the predominant species present, that is, on a molar basis it is more abundant than any other individual species in the same mixture. In certain embodiments, a substantially pure molecule is a composition wherein the object species comprises at least 50% (on a molar basis) of all macromolecular species present. In other embodiments, a substantially pure composition will comprise at least 80%, 85%, 90%, 95%, or 99% of all macromolecular species present in the composition. In other embodiments, the object species is purified to essential homogeneity wherein contaminating species cannot be detected in the composition by conventional detection methods and thus the composition consists of a single detectable macromolecular species.

The terms "treat" and "treating" refer to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, certain methods presented herein can be employed to treat Type 2 diabetes, obesity and/or dyslipidemia, either prophylactically or as an acute treatment, to decrease plasma glucose levels, to decrease circulating triglyceride levels, to decrease circulating cholesterol levels and/or ameliorate a symptom associated with type 2 diabetes, obesity and dyslipidemia.

An "effective amount" is generally an amount sufficient to reduce the severity and/or frequency of symptoms, eliminate the symptoms and/or underlying cause, prevent the occurrence of symptoms and/or their underlying cause, and/or improve or remediate the damage that results from or is associated with diabetes, obesity and dyslipidemia. In some embodiments, the effective amount is a therapeutically effective amount or a prophylactically effective amount. A "therapeutically effective amount" is an amount sufficient to remedy a disease state (e.g., diabetes, obesity or dyslipidemia) or symptoms, particularly a state or symptoms associated with the disease state, or otherwise prevent, hinder, retard or reverse the progression of the disease state or any other undesirable symptom associated with the disease in any way whatsoever. A "prophylactically effective amount" is an amount of a pharmaceutical composition that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of diabetes, obesity or dyslipidemia, or reducing the likelihood of the onset (or reoccurrence) of diabetes, obesity or dyslipidemia or associated symptoms. The full therapeutic or prophylactic effect does not necessarily occur by administration of one dose, and can occur only after administration of a series of doses. Thus, a therapeutically or prophylactically effective amount can be administered in one or more administrations.

"Amino acid" takes its normal meaning in the art. The twenty naturally-occurring amino acids and their abbreviations follow conventional usage. See, Immunology-A Synthesis, 2[nd] Edition, (E. S. Golub and D. R. Green, eds.), Sinauer Associates: Sunderland, Mass. (1991), incorporated herein by reference for any purpose. Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural or non-naturally occurring amino acids such as α-,α-disubstituted amino acids, N-alkyl amino acids, and other unconventional amino acids can also be suitable components for polypeptides and are included in the phrase "amino acid." Examples of non-naturally amino acids (which can be substituted for any naturally-occurring amino acid found in any sequence disclosed herein, as desired) include: 4-hydroxyproline, γ-carboxyglutamate, ϵ-N,N,N-trimethyllysine, ϵ-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ-N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxyl-terminal direction, in accordance with standard usage and convention. A non-limiting lists of examples of non-naturally occurring amino acids that can be inserted into an antigen binding protein sequence or substituted for a wild-type residue in an antigen binding sequence include β-amino acids, homoamino acids, cyclic amino acids and amino acids with derivatized side chains. Examples include (in the L-form or D-form; abbreviated as in parentheses): citrulline (Cit), homocitrulline (hCit), Nα-methylcitrulline (NMeCit), Nα-methylhomocitrulline (Nα-MeHoCit), ornithine (Orn), Nα-Methylornithine (Nα-MeOrn or NMeOrn), sarcosine (Sar), homolysine (hLys or hK), homoarginine (hArg or hR), homoglutamine (hQ), Nα-methylarginine (NMeR), Nα-methylleucine (Nα-MeL or NMeL), N-methylhomolysine (NMeHoK), Nα-methylglutamine (NMeQ), norleucine (Nle), norvaline (Nva), 1,2,3,4-tetrahydroisoquinoline (Tic), Octahydroindole-2-carboxylic acid (Oic), 3-(1-naphthyl)alanine (1-Nal), 3-(2-naphthyl)alanine (2-Nal), 1,2,3,4-tetrahydroisoquinoline (Tic), 2-indanylglycine (IgI), para-iodophenylalanine (pI-Phe), para-aminophenylalanine (4AmP or 4-Amino-Phe), 4-guanidino phenylalanine (Guf), glycyllysine (abbreviated "K(Nϵ-glycyl)" or "K(glycyl)" or "K(gly)"), nitrophenylalanine (nitrophe), aminophenylalanine (aminophe or Amino-Phe), benzylphenylalanine (benzylphe), γ-carboxyglutamic acid (γ-carboxyglu), hydroxyproline (hydroxypro), p-carboxyl-phenylalanine (Cpa), α-aminoadipic acid (Aad), Nα-methyl valine (NMeVal), N-α-methyl leucine (NMeLeu), Nα-methylnorleucine (NMeNle), cyclopentylglycine (Cpg), cyclohexylglycine (Chg), acetylarginine (acetylarg), α, β-diaminopropionoic acid (Dpr), α, γ-diaminobutyric acid (Dab), diaminopropionic acid (Dap), cyclohexylalanine (Cha), 4-methyl-phenylalanine (MePhe), β, β-diphenyl-alanine (BiPhA), aminobutyric acid (Abu), 4-phenyl-phenylalanine (or biphenylalanine; 4Bip), α-amino-isobutyric acid (Aib), beta-alanine, beta-aminopropionic acid, piperidinic acid, aminocaprioic acid, aminoheptanoic acid, aminopimelic acid, desmosine, diaminopimelic acid, N-ethylglycine, N-ethylaspargine, hydroxylysine, allo-hydroxylysine, isodesmosine, allo-isoleucine, N-methylglycine, N-methylisoleucine, N-methylvaline, 4-hydroxyproline (Hyp), γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, ω-methylarginine, 4-Amino-O-Phthalic Acid (4APA), and other similar amino acids, and derivatized forms of any of those specifically listed.

II. General Overview

Antigen-binding proteins that bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, are provided herein. A unique property of the antigen binding proteins disclosed herein is the agonistic nature of these proteins, specifically the ability to mimic the in vivo effect of FGF21 and to induce FGF21-like signaling. More remarkably and specifically, some of the antigen binding proteins disclosed herein induce FGF21-like signaling in several in vitro cell-based assay, including the ELK-luciferase reporter assay of Example 5 under the following conditions: (1) the binding to and activity of the FGF21 receptor is β-Klotho dependent; (2) the activity is selective to FGFR1c/βKlotho complex; (3) the binding to the FGFR1c/βKlotho triggers FGF21-like signaling pathways; and (4) the potency (EC50) is comparable to a wild-type FGF21 standard comprising the mature form of SEQ ID NO:2, as measured in the following cell-based assays: (1) the recombinant FGF21 receptor mediated luciferase-reporter cell assay of Example 5; (2) the ERK-phosphorylation in the recombinant FGF21 receptor mediated cell assay of Example 5; and (3) ERK-phosphorylation in human adipocytes as described in more details in Example 7. The disclosed antigen binding proteins, therefore, are expected to exhibit activities in vivo that are consistent with the natural biological function of FGF21. This property makes the disclosed antigen binding proteins viable therapeutics for the treatment of metabolic diseases such as type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, metabolic syndrome and broadly any disease or condition in which it is desirable to mimic or augment the in vivo effects of FGF21.

In some embodiments of the present disclosure the antigen binding proteins provided can comprise polypeptides into which one or more complementary determining regions (CDRs) can be embedded and/or joined. In such antigen binding proteins, the CDRs can be embedded into a "framework" region, which orients the CDR(s) such that the proper antigen binding properties of the CDR(s) is achieved. In general, such antigen binding proteins that are provided can facilitate or enhance the interaction between FGFR1c and β-Klotho, and can substantially induce FGF21-like signaling.

Certain antigen binding proteins described herein are antibodies or are derived from antibodies. In certain embodiments, the polypeptide structure of the antigen binding proteins is based on antibodies, including, but not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as "antibody mimetics"), chimeric antibodies, humanized antibodies, human antibodies, antibody fusions (sometimes referred to herein as "antibody conjugates"), hemibodies and fragments thereof. The various structures are further described herein below.

The antigen binding proteins provided herein have been demonstrated to bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, and particularly to (i) human β-Klotho; (ii) human FGFR1c, human FGFR2c, human FGFR3c or human FGFR4; or (iii) a complex comprising human β-Klotho and one of human FGFR1c, human FGFR2c, human FGFR3c, and human FGFR4. As described and shown in the Examples presented herein, based the Western blot results, commercially-available anti-β-Klotho or anti-FGFR1c antibodies bind to denatured β-Klotho or FGFR1c whereas the antigen binding protein (agonistic antibodies) do not. Conversely, the provided antigen binding proteins recognize the native structure of the FGFR1c and β-Klotho on the cell surface whereas the commercial antibodies do not, based on the FACS results provided. See Example 9. The antigen binding proteins that are provided therefore mimic the natural in vivo biological activity of FGF21. As a consequence, the antigen binding proteins provided herein are capable of activating FGF21-like signaling activity. In particular, the disclosed antigen binding proteins can have one or more of the following activities in vivo: induction of FGF21-like signal transduction pathways, lowering blood glucose levels, lowering circulating lipid levels, improving metabolic parameters and other physiological effects induced in vivo by the formation of the ternary complex of FGFR1c, β-Klotho and FGF21, for example in conditions such as type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome.

The antigen binding proteins that specifically bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are disclosed herein have a variety of utilities. Some of the antigen binding proteins, for instance, are useful in specific binding assays, in the affinity purification of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, including the human forms of these disclosed proteins, and in screening assays to identify other agonists of FGF21-like signaling activity.

The antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are disclosed herein can be used in a variety of treatment applications, as explained herein. For example, certain antigen binding proteins are useful for treating conditions associated with FGF21-like signaling processes in a patient, such as reducing, alleviating, or treating type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome. Other uses for the antigen binding proteins include, for example, diagnosis of diseases or conditions associated with β-Klotho, FGFR1c, FGFR2c, FGFR3c, FGFR4 or FGF21, and screening assays to determine the presence or absence of these molecules. Some of the antigen binding proteins described herein can be useful in treating conditions, symptoms and/or the pathology associated with decreased FGF21-like signaling activity. Exemplary conditions include, but are not limited to, diabetes, obesity, NASH and dyslipidemia.

FGF21

The antigen binding proteins disclosed herein induce FGF21-mediated signaling, as defined herein. In vivo, the mature form of FGF21 is the active form of the molecule. The nucleotide sequence encoding full length FGF21 is provided; the nucleotides encoding the signal sequence are underlined.

(SEQ ID NO: 1)

ATG GAC TCG GAC GAG ACC GGG TTC GAG CAC TCA GGA CTG TGG GTT TCT GTG

CTG GCT GGT CTT CTG CTG GGA GCC TGC CAG GCA CAC CCC ATC CCT GAC TCC

AGT CCT CTC CTG CAA TTC GGG GGC CAA GTC CGG CAG CGG TAC CTC TAC ACA

GAT GAT GCC CAG CAG ACA GAA GCC CAC CTG GAG ATC AGG GAG GAT GGG

ACG GTG GGG GGC GCT GCT GAC CAG AGC CCC GAA AGT CTC CTG CAG CTG

AAA GCC TTG AAG CCG GGA GTT ATT CAA ATC TTG GGA GTC AAG ACA TCC

AGG TTC CTG TGC CAG CGG CCA GAT GGG GCC CTG TAT GGA TCG CTC CAC TTT

GAC CCT GAG GCC TGC AGC TTC CGG GAG CTG CTT CTT GAG GAC GGA TAC AAT

GTT TAC CAG TCC GAA GCC CAC GGC CTC CCG CTG CAC CTG CCA GGG AAC AAG

TCC CCA CAC CGG GAC CCT GCA CCC CGA GGA CCA GCT CGC TTC CTG CCA CTA

CCA GGC CTG CCC CCC GCA CCC CCG GAG CCA CCC GGA ATC CTG GCC CCC CAG

CCC CCC GAT GTG GGC TCC TCG GAC CCT CTG AGC ATG GTG GGA CCT TCC CAG

GGC CGA AGC CCC AGC TAC GCT TCC TGA

The amino acid sequence of full length FGF21 is provided; the amino acids that make up the signal sequence are underlined:

(SEQ ID NO: 2)

M D S D E T G F E H S G L W V S V L A G L L L G A C Q A H P I P D S S P L L Q F G G Q

V R Q R Y L Y T D D A Q Q T E A H L E I R E D G T V G G A A D Q S P E S L L Q L K A

L K P G V I Q I L G V K T S R F L C Q R P D G A L Y G S L H F D P E A C S F R E L L L E

D G Y N V Y Q S E A H G L P L H L P G N K S P H R D P A P R G P A R F L P L P G L P P

A P P E P P G I L A P Q P P D V G S S D P L S M V G P S Q G R S P S Y A S

FGFR1c

The antigen binding proteins disclosed herein bind to FGFR1c, in particular human FGFR1c, when associated with β-Klotho. The nucleotide sequence encoding human FGFR1c (GenBank™ Accession Number NM_023110) is provided:

(SEQ ID NO: 3)

ATGTGGAGCTGGAAGTGCCTCCTCTTCTGGGCTGTGCTGGTCACAGCC

ACACTCTGCACCGCTAGGCCGTCCCCGACCTTGCCTGAACAAGCCCAG

CCCTGGGGAGCCCCTGTGGAAGTGGAGTCCTTCCTGGTCCACCCCGGT

GACCTGCTGCAGCTTCGCTGTCGGCTGCGGGACGATGTGCAGAGCATC

AACTGGCTGCGGGACGGGGTGCAGCTGGCGGAAAGCAACCGCACCCG

CATCACAGGGGAGGAGGTGGAGGTGCAGGACTCCGTGCCCGCAGACT

CCGGCCTCTATGCTTGCGTAACCAGCAGCCCCTCGGGCAGTGACACCA

CCTACTTCTCCGTCAATGTTTCAGATGCTCTCCCCTCCTCGGAGGATGA

TGATGATGATGATGACTCCTCTTCAGAGGAGAAAGAAACAGATAACA

CCAAACCAAACCGTATGCCCGTAGCTCCATATTGGACATCACCAGAAA

AGATGGAAAAGAAATTGCATGCAGTGCCGGCTGCCAAGACAGTGAAG

TTCAAATGCCCTTCCAGTGGGACACCAAACCCAACACTGCGCTGGTTG

-continued

AAAAATGGCAAAGAATTCAAACCTGACCACAGAATTGGAGGCTACAA

GGTCCGTTATGCCACCTGGAGCATCATAATGGACTCTGTGGTGCCCTC

TGACAAGGGCAACTACACCTGCATTGTGGAGAATGAGTACGGCAGCA

TCAACCACACATACCAGCTGGATGTCGTGGAGCGGTCCCCTCACCGGC

CCATCCTGCAAGCAGGGTTGCCCGCCAACAAAACAGTGGCCCTGGGT

AGCAACGTGGAGTTCATGTGTAAGGTGTACAGTGACCCGCAGCCGCAC

ATCCAGTGGCTAAAGCACATCGAGGTGAATGGGAGCAAGATTGGCCC

AGACAACCTGCCTTATGTCCAGATCTTGAAGACTGCTGGAGTTAATAC

CACCGACAAAGAGATGGAGGTGCTTCACTTAAGAAATGTCTCCTTTGA

GGACGCAGGGGAGTATACGTGCTTGGCGGGTAACTCTATCGGACTCTC

CCATCACTCTGCATGGTTGACCGTTCTGGAAGCCCTGGAAGAGAGGCC

GGCAGTGATGACCTCGCCCCTGTACCTGGAGATCATCATCTATTGCAC

AGGGGCCTTCCTCATCTCCTGCATGGTGGGGTCGGTCATCGTCTACAA

GATGAAGAGTGGTACCAAGAAGAGTGACTTCCACAGCCAGATGGCTG

TGCACAAGCTGGCCAAGAGCATCCCTCTGCGCAGACAGGTAACAGTG

TCTGCTGACTCCAGTGCATCCATGAACTCTGGGGTTCTTCTGGTTCGGC

CATCACGGCTCTCCTCCAGTGGGACTCCCATGCTAGCAGGGGTCTCTG

-continued

AGTATGAGCTTCCCGAAGACCCTCGCTGGGAGCTGCCTCGGGACAGAC

TGGTCTTAGGCAAACCCCTGGGAGAGGGCTGCTTTGGGCAGGTGGTGT

TGGCAGAGGCTATCGGGCTGGACAAGGACAAACCCAACCGTGTGACC

AAAGTGGCTGTGAAGATGTTGAAGTCGGACGCAACAGAGAAAGACTT

GTCAGACCTGATCTCAGAAATGGAGATGATGAAGATGATCGGGAAGC

ATAAGAATATCATCAACCTGCTGGGGGCCTGCACGCAGGATGGTCCCT

TGTATGTCATCGTGGAGTATGCCTCCAAGGGCAACCTGCGGGAGTACC

TGCAGGCCCGGAGGCCCCCAGGGCTGGAATACTGCTACAACCCCAGC

CACAACCCAGAGGAGCAGCTCTCCTCCAAGGACCTGGTGTCCTGCGCC

TACCAGGTGGCCCGAGGCATGGAGTATCTGGCCTCCAAGAAGTGCATA

CACCGAGACCTGGCAGCCAGGAATGTCCTGGTGACAGAGGACAATGT

GATGAAGATAGCAGACTTTGGCCTCGCACGGGACATTCACCACATCGA

CTACTATAAAAAGACAACCAACGGCCGACTGCCTGTGAAGTGGATGG

CACCCGAGGCATTATTTGACCGGATCTACACCCACCAGAGTGATGTGT

GGTCTTTCGGGGTGCTCCTGTGGGAGATCTTCACTCTGGGCGGCTCCCC

ATACCCCGGTGTGCCTGTGGAGGAACTTTTCAAGCTGCTGAAGGAGGG

TCACCGCATGGACAAGCCCAGTAACTGCACCAACGAGCTGTACATGAT

GATGCGGGACTGCTGGCATGCAGTGCCCTCACAGAGACCCACCTTCAA

GCAGCTGGTGGAAGACCTGGACCGCATCGTGGCCTTGACCTCCAACCA

GGAGTACCTGGACCTGTCCATGCCCCTGGACCAGTACTCCCCCAGCTT

TCCCGACACCCGGAGCTCTACGTGCTCCTCAGGGGAGGATTCCGTCTT

CTCTCATGAGCCGCTGCCCGAGGAGCCCTGCCTGCCCCGACACCCAGC

CCAGCTTGCCAATGGCGGACTCAAACGCCGCTGA.

The amino acid sequence of human FGFR1c (GenBank™ Accession Number NP_075598)is provided:

(SEQ ID NO: 4)

MWSWKCLLFWAVLVTATLCTARPSPTLPEQAQPWGAPVEVESFLVHPG

DLLQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADSGL

YACVTSSPSGSDTTYFSVNVSDALPSSEDDDDDDDSSSEEKETDNTKPNR

MPVAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEF

KPDHRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEYGSINHTYQLDV

VERSPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNG

SKIGPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSI

GLSHHSAWLTVLEALEERPAVMTSPLYLEIIIYCTGAFLISCMVGSVIVY

KMKSGTKKSDFHSQMAVHKLAKSIPLRRQVTVSADSSASMNSGVLLVRPS

RLSSSGTPMLAGVSEYELPEDPRWELPRDRLVLGKPLGEGCFGQVVLAEA

IGLDKDKPNRVTKVAVKMLKSDATEKDLSDLISEMEMMKMIGKHKNIIN

LLGACTQDGPLYVIVEYASKGNLREYLQARRPPGLEYCYNPSHNPEEQLS

SKDLVSCAYQVARGMEYLASKKCIHRDLAARNVLVTEDNVMKIADFGL

ARDIHHIDYYKKTTNGRLPVKWMAPEALFDRIYTHQSDVWSFGVLLWEI

FTLGGSPYPGVPVEELFKLLKEGHRMDKPSNCTNELYMMMRDCWHAVP

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SQRPTFKQLVEDLDRIVALTSNQEYLDLSMPLDQYSPSFPDTRSSTCSSG

EDSVFSHEPLPEEPCLPRHPAQLANGGLKRR.

The antigen binding proteins described herein bind the extracellular portion of FGFR1c. An example of an extracellular region of FGFR1c is:

(SEQ ID NO: 5)

MWSWKCLLFWAVLVTATLCTARPSPTLPEQAQPWGAPVEVESFLVHPGDL

LQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADSGLYA

CVTSSPSGSDTTYFSVNVSDALPSSEDDDDDDDSSSEEKETDNTKPNRMP

VAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEFKPD

HRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEYGSINHTYQLDVVER

SPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKI

GPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLS

HHSAWLTVLEALEERPAVMTSPLY.

As described herein, FGFR1c proteins can also include fragments. As used herein, the terms are used interchangeably to mean a receptor, in particular and unless otherwise specified, a human receptor, that upon association with β-Klotho and FGF21 induces FGF21-like signaling activity.

The term FGFR1c also includes post-translational modifications of the FGFR1c amino acid sequence, for example, possible N-linked glycosylation sites. Thus, the antigen binding proteins can bind to or be generated from proteins glycosylated at one or more of the positions.

β-Klotho

The antigen binding proteins disclosed herein bind to β-Klotho, in particular human β-Klotho. The nucleotide sequence encoding human β-Klotho (GenBank™ Accession Number NM_175737) is provided:

(SEQ ID NO: 6)

ATGAAGCCAGGCTGTGCGGCAGGATCTCCAGGGAATGAATGGATTTTC

TTCAGCACTGATGAAATAACCACACGCTATAGGAATACAATGTCCAAC

GGGGGATTGCAAAGATCTGTCATCCTGTCAGCACTTATTCTGCTACGA

GCTGTTACTGGATTCTCTGGAGATGGAAGAGCTATATGGTCTAAAAAT

CCTAATTTTACTCCGGTAAATGAAAGTCAGCTGTTTCTCTATGACACTT

TCCCTAAAAACTTTTTCTGGGGTATTGGGACTGGAGCATTGCAAGTGG

AAGGGAGTTGGAAGAAGGATGGAAAAGGACCTTCTATATGGGATCAT

TTCATCCACACACACCTTAAAAATGTCAGCAGCACGAATGGTTCCAGT

GACAGTTATATTTTTCTGGAAAAAGACTTATCAGCCCTGGATTTTATAG

GAGTTTCTTTTTATCAATTTTCAATTTCCTGGCCAAGGCTTTTCCCCGAT

GGAATAGTAACAGTTGCCAACGCAAAAGGTCTGCAGTACTACAGTACT

CTTCTGGACGCTCTAGTGCTTAGAAACATTGAACCTATAGTTACTTTAT

ACCACTGGGATTTGCCTTTGGCACTACAAGAAAAATATGGGGGGTGGA

AAAATGATACCATAATAGATATCTTCAATGACTATGCCACATACTGTT

TCCAGATGTTTGGGGACCGTGTCAAATATTGGATTACAATTCACAACC

CATATCTAGTGGCTTGGCATGGGTATGGGACAGGTATGCATGCCCCTG

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GAGAGAAGGGAAATTTAGCAGCTGTCTACACTGTGGGACACAACTTG
ATCAAGGCTCACTCGAAAGTTTGGCATAACTACAACACACATTTCCGC
CCACATCAGAAGGGTTGGTTATCGATCACGTTGGGATCTCATTGGATC
GAGCCAAACCGGTCGGAAAACACGATGGATATATTCAAATGTCAACA
ATCCATGGTTTCTGTGCTTGGATGGTTTGCCAACCCTATCCATGGGGAT
GGCGACTATCCAGAGGGGATGAGAAAGAAGTTGTTCTCCGTTCTACCC
ATTTTCTCTGAAGCAGAGAAGCATGAGATGAGAGGCACAGCTGATTTC
TTTGCCTTTTCTTTTGGACCCAACAACTTCAAGCCCCTAAACACCATGG
CTAAAATGGGACAAAATGTTTCACTTAATTTAAGAGAAGCGCTGAACT
GGATTAAACTGGAATACAACAACCCTCGAATCTTGATTGCTGAGAATG
GCTGGTTCACAGACAGTCGTGTGAAAACAGAAGACACCACGGCCATC
TACATGATGAAGAATTTCCTCAGCCAGGTGCTTCAAGCAATAAGGTTA
GATGAAATACGAGTGTTTGGTTATACTGCCTGGTCTCTCCTGGATGGCT
TTGAATGGCAGGATGCTTACACCATCCGCCGAGGATTATTTTATGTGG
ATTTTAACAGTAAACAGAAAGAGCGGAAACCTAAGTCTTCAGCACACT
ACTACAAACAGATCATACGAGAAAATGGTTTTTCTTTAAAAGAGTCCA
CGCCAGATGTGCAGGGCCAGTTTCCCTGTGACTTCTCCTGGGGTGTCA
CTGAATCTGTTCTTAAGCCCGAGTCTGTGGCTTCGTCCCCACAGTTCAG
CGATCCTCATCTGTACGTGTGGAACGCCACTGGCAACAGACTGTTGCA
CCGAGTGGAAGGGGTGAGGCTGAAAACACGACCCGCTCAATGCACAG
ATTTTGTAAACATCAAAAAACAACTTGAGATGTTGGCAAGAATGAAA
GTCACCCACTACCGGTTTGCTCTGGATTGGGCCTCGGTCCTTCCCACTG
GCAACCTGTCCGCGGTGAACCGACAGGCCCTGAGGTACTACAGGTGC
GTGGTCAGTGAGGGGCTGAAGCTTGGCATCTCCGCGATGGTCACCCTG
TATTATCCGACCCACGCCCACCTAGGCCTCCCCGAGCCTCTGTTGCAT
GCCGACGGGTGGCTGAACCCATCGACGGCCGAGGCCTTCCAGGCCTA
CGCTGGGCTGTGCTTCCAGGAGCTGGGGGACCTGGTGAAGCTCTGGAT
CACCATCAACGAGCCTAACCGGCTAAGTGACATCTACAACCGCTCTGG
CAACGACACCTACGGGGCGGCGCACAACCTGCTGGTGGCCCACGCCC
TGGCCTGGCGCCTCTACGACCGGCAGTTCAGGCCCTCACAGCGCGGGG
CCGTGTCGCTGTCGCTGCACGCGGACTGGGCGGAACCCGCCAACCCCT
ATGCTGACTCGCACTGGAGGGCGGCCGAGCGCTTCCTGCAGTTCGAGA
TCGCCTGGTTCGCCGAGCCGCTCTTCAAGACCGGGGACTACCCCGCGG
CCATGAGGGAATACATTGCCTCCAAGCACCGACGGGGGCTTTCCAGCT
CGGCCCTGCCGCGCCTCACCGAGGCCGAAAGGAGGCTGCTCAAGGGC
ACGGTCGACTTCTGCGCGCTCAACCACTTCACCACTAGGTTCGTGATG
CACGAGCAGCTGGCCGGCAGCCGCTACGACTCGGACAGGGACATCCA
GTTTCTGCAGGACATCACCCGCCTGAGCTCCCCCACGCGCCTGGCTGT
GATTCCCTGGGGGGTGCGCAAGCTGCTGCGGTGGGTCCGGAGGAACT
ACGGCGACATGGACATTTACATCACCGCCAGTGGCATCGACGACCAG

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GCTCTGGAGGATGACCGGCTCCGGAAGTACTACCTAGGGAAGTACCTT
CAGGAGGTGCTGAAAGCATACCTGATTGATAAAGTCAGAATCAAAGG
CTATTATGCATTCAAACTGGCTGAAGAGAAATCTAAACCCAGATTTGG
ATTCTTCACATCTGATTTTAAAGCTAAATCCTCAATACAATTTTACAAC
AAAGTGATCAGCAGCAGGGGCTTCCCTTTTGAGAACAGTAGTTCTAGA
TGCAGTCAGACCCAAGAAAATACAGAGTGCACTGTCTGCTTATTCCTT
GTGCAGAAGAAACCACTGATATTCCTGGGTTGTTGCTTCTTCTCCACCC
TGGTTCTACTCTTATCAATTGCCATTTTTCAAAGGCAGAAGAGAAGAA
AGTTTTGGAAAGCAAAAAACTTACAACACATACCATTAAAGAAAGGC
AAGAGAGTTGTTAGCTAA.

The amino acid sequence of full length human β-Klotho (GenBank™ Accession Number NP_783864) is provided:

(SEQ ID NO: 7)
MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL
ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
QIIRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHL
YVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA
LDWASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLG
LPEPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDI
YNRSGNDTYGAAHNLLVAHALAWRLYDRQFRPSQRGAVSLSLHADWAEPA
NPYADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSS
SALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFL
QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD
RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK
AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS.

The antigen binding proteins described herein bind the extracellular portion of β-Klotho. An example of an extracellular region of β-Klotho is:

(SEQ ID NO: 8.)
MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ

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FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL

ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY

GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL

GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS

VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL

NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD

EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK

QIIRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHL

YVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA

LDWASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLG

LPEPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDI

YNRSGNDTYGAAHNLLVAHALAWRLYDRQFRPSQRGAVSLSLHADWAEPA

NPYADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSS

SALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFL

QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD

RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK

AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKP
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The murine form of β-Klotho, and fragments and subsequences thereof, can be of use in studying and/or constructing the molecules provided herein. The nucleotide sequence encoding murine β-Klotho (GenBank™ Accession Number NM_031180) is provided:

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                                          (SEQ ID NO: 469)
ATGAAGACAGGCTGTGCAGCAGGGTCTCCGGGGAATGAATGGATTTTCTT

CAGCTCTGATGAAAGAAACACACGCTCTAGGAAAACAATGTCCAACAGGG

CACTGCAAAGATCTGCCGTGCTGTCTGCGTTTGTTCTGCTGCGAGCTGTT

ACCGGCTTCTCCGGAGACGGGAAAGCAATATGGGATAAAAAACAGTACGT

GAGTCCGGTAAACCCAAGTCAGCTGTTCCTCTATGACACTTTCCCTAAAA

ACTTTTCCTGGGGCGTTGGGACCGGAGCATTTCAAGTGGAAGGGAGTTGG

AAGACAGATGGAAGAGGACCCTCGATCTGGGATCGGTACGTCTACTCACA

CCTGAGAGGTGTCAACGGCACAGACAGATCCACTGACAGTTACATCTTTC

TGGAAAAAGACTTGTTGGCTCTGGATTTTTTAGGAGTTTCTTTTTATCAG

TTCTCAATCTCCTGGCCACGGTTGTTTCCCAATGGAACAGTAGCAGCAGT

GAATGCGCAAGGTCTCCGGTACTACCGTGCACTTCTGGACTCGCTGGTAC

TTAGGAATATCGAGCCCATTGTTACCTTGTACCATTGGGATTTGCCTCTG

ACGCTCCAGGAAGAATATGGGGGCTGGAAAAATGCAACTATGATAGATCT

CTTCAACGACTATGCCACATACTGCTTCCAGACCTTTGGAGACCGTGTCA

AATATTGGATTACAATTCACAACCCTTACCTTGTTGCTTGGCATGGGTTT

GGCACAGGTATGCATGCACCAGGAGAGAAGGGAAATTTAACAGCTGTCTA

CACTGTGGGACACAACCTGATCAAGGCACATTCGAAAGTGTGGCATAACT

ACGACAAAAACTTCCGCCCTCATCAGAAGGGTTGGCTCTCCATCACCTTG

GGGTCCCATTGGATAGAGCCAAACAGAACAGACAACATGGAGGACGTGAT
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CAACTGCCAGCACTCCATGTCCTCTGTGCTTGGATGGTTCGCCAACCCCA

TCCACGGGGACGGCGACTACCCTGAGTTCATGAAGACGGGCGCCATGATC

CCCGAGTTCTCTGAGGCAGAGAAGGAGGAGGTGAGGGGCACGGCTGATTT

CTTTGCCTTTTCCTTCGGGCCCAACAACTTCAGGCCCTCAAACACCGTGG

TGAAAATGGGACAAAATGTATCACTCAACTTAAGGCAGGTGCTGAACTGG

ATTAAACTGGAATACGATGACCCTCAAATCTTGATTTCGGAGAACGGCTG

GTTCACAGATAGCTATATAAAGACAGAGGACACCACGGCCATCTACATGA

TGAAGAATTTCCTAAACCAGGTTCTTCAAGCAATAAAATTTGATGAAATC

CGCGTGTTTGGTTATACGGCCTGGACTCTCCTGGATGGCTTTGAGTGGCA

GGATGCCTATACGACCCGACGAGGGCTGTTTTATGTGGACTTTAACAGTG

AGCAGAAAGAGAGGAAACCCAAGTCCTCGGCTCATTACTACAAGCAGATC

ATACAAGACAACGGCTTCCCTTTGAAAGAGTCCACGCCAGACATGAAGGG

TCGGTTCCCCTGTGATTTCTCTTGGGGAGTCACTGAGTCTGTTCTTAAGC

CCGAGTTTACGGTCTCCTCCCCGCAGTTTACCGATCCTCACCTGTATGTG

TGGAATGTCACTGGCAACAGATTGCTCTACCGAGTGGAAGGGGTAAGGCT

GAAAACAAGACCATCCCAGTGCACAGATTATGTGAGCATCAAAAAACGAG

TTGAAATGTTGGCAAAAATGAAAGTCACCCACTACCAGTTTGCTCTGGAC

TGGACCTCTATCCTTCCCACTGGCAATCTGTCCAAAGTTAACAGACAAGT

GTTAAGGTACTATAGGTGTGTGGTGAGCGAAGGACTGAAGCTGGGCGTCT

TCCCCATGGTGACGTTGTACCACCCAACCCACTCCCATCTCGGCCTCCCC

CTGCCACTTCTGAGCAGTGGGGGGTGGCTAAACATGAACACAGCCAAGGC

CTTCCAGGACTACGCTGAGCTGTGCTTCCGGGAGTTGGGGGACTTGGTGA

AGCTCTGGATCACCATCAATGAGCCTAACAGGCTGAGTGACATGTACAAC

CGCACGAGTAATGACACCTACCGTGCAGCCCACAACCTGATGATCGCCCA

TGCCCAGGTCTGGCACCTCTATGATAGGCAGTATAGGCCGGTCCAGCATG

GGGCTGTGTCGCTGTCCTTACATTGCGACTGGGCAGAACCTGCCAACCCC

TTTGTGGATTCACACTGGAAGGCAGCCGAGCGCTTCCTCCAGTTTGAGAT

CGCCTGGTTTGCAGATCCGCTCTTCAAGACTGGCGACTATCCATCGGTTA

TGAAGGAATACATCGCCTCCAAGAACCAGCGAGGGCTGTCTAGCTCAGTC

CTGCCGCGCTTCACCGCGAAGGAGAGCAGGCTGGTGAAGGGTACCGTCGA

CTTCTACGCACTGAACCACTTCACTACGAGGTTCGTGATACACAAGCAGC

TGAACACCAACCGCTCAGTTGCAGACAGGGACGTCCAGTTCCTGCAGGAC

ATCACCCGCCTAAGCTCGCCCAGCCGCCTGGCTGTAACACCCTGGGGAGT

GCGCAAGCTCCTTGCGTGGATCCGGAGGAACTACAGAGACAGGGATATCT

ACATCACAGCCAATGGCATCGATGACCTGGCTCTAGAGGATGATCAGATC

CGAAAGTACTACTTGGAGAAGTATGTCCAGGAGGCTCTGAAAGCATATCT

CATTGACAAGGTCAAAATCAAAGGCTACTATGCATTCAAACTGACTGAAG

AGAAATCTAAGCCTAGATTTGGATTTTTCACCTCTGACTTCAGAGCTAAG

TCCTCTGTCCAGTTTTACAGCAAGCTGATCAGCAGCAGTGGCCTCCCCGC

TGAGAACAGAAGTCCTGCGTGTGGTCAGCCTGCGGAAGACACAGACTGCA
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CCATTTGCTCATTTCTCGTGGAGAAGAAACCACTCATCTTCTTCGGTTGC

TGCTTCATCTCCACTCTGGCTGTACTGCTATCCATCACCGTTTTTCATCA

TCAAAAGAGAAGAAAATTCCAGAAAGCAAGGAACTTACAAAATATACCAT

TGAAGAAAGGCCACAGCAGAGTTTTCAGCTAA
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The amino acid sequence of full length murine β-Klotho (GenBank™ Accession Number NP_112457) is provided:

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                                          (SEQ ID NO: 468)
MKTGCAAGSPGNEWIFFSSDERNTRSRKTMSNRALQRSAVLSAFVLLRA

VTGFSGDGKAIWDKKQYVSPVNPSQLFLYDTFPKNFSWGVGTGAFQVEG

SWKTDGRGPSIWDRYVYSHLRGVNGTDRSTDSYIFLEKDLLALDFLGVSF

YQFSISWPRLFPNGTVAAVNAQGLRYYRALLDSLVLRNIEPIVTLYHWDL

PLTLQEEYGGWKNATMIDLFNDYATYCFQTFGDRVKYWITIHNPYLVAW

HGFGTGMHAPGEKGNLTAVYTVGHNLIKAHSKVWHNYDKNFRPHQKG

WLSITLGSHWIEPNRTDNMEDVINCQHSMSSVLGWFANPIHGDGDYPEF

MKTGAMIPEFSEAEKEEVRGTADFFAFSFGPNNFRPSNTVVKMGQNVSLN

LRQVLNWIKLEYDDPQILISENGWFTDSYIKTEDTTAIYMMKNFLNQVLQ

AIKFDEIRVFGYTAWTLLDGFEWQDAYTTRRGLFYVDFNSEQKERKPKSS

AHYYKQIIQDNGFPLKESTPDMKGRFPCDFSWGVTESVLKPEFTVSSPQF

TDPHLYVWNVTGNRLLYRVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKV

THYQFALDWTSILPTGNLSKVNRQVLRYYRCVVSEGLKLGVFPMVTLYH

PTHSHLGLPLPLLSSGGWLNMNTAKAFQDYAELCFRELGDLVKLWITINE

PNRLSDMYNRTSNDTYRAAHNLMIAHAQVWHLYDRQYRPVQHGAVSLS

LHCDWAEPANPFVDSHWKAAERFLQFEIAWFADPLFKTGDYPSVMKEYI

ASKNQRGLSSSVLPRFTAKESRLVKGTVDFYALNHFTTRFVIHKQLNTNR

SVADRDVQFLQDITRLSSPSRLAVTPWGVRKLLAWIRRNYRDRDIYITAN

GIDDLALEDDQIRKYYLEKYVQEALKAYLIDKVKIKGYYAFKLTEEKSKP

RFGFFTSDFRAKSSVQFYSKLISSSGLPAENRSPACGQPAEDTDCTICSF

LVEKKPLIFFGCCFISTLAVLLSITVFHHQKRRKFQKARNLQNIPLKKGH

SRVFS
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As described herein, β-Klotho proteins can also include fragments. As used herein, the terms are used interchangeably to mean a co-receptor, in particular and unless otherwise specified, a human co-receptor, that upon association with FGFR1c and FGF21 induces FGF21-like signaling activity.

The term β-Klotho also includes post-translational modifications of the β-Klotho amino acid sequence, for example, possible N-linked glycosylation sites. Thus, the antigen binding proteins can bind to or be generated from proteins glycosylated at one or more of the positions.

Antigen Binding Proteins that Specifically Bind One or More of β-Klotho, FGFR1c, FGFR2c, FGFR3c, FGFR4c

A variety of selective binding agents useful for modulating FGF21-like signaling are provided. These agents include, for instance, antigen binding proteins that contain an antigen binding domain (e.g., single chain antibodies, domain antibodies, hemibodies, immunoadhesions, and polypeptides with an antigen binding region) and specifically bind to FGFR1c, β-Klotho or both FGFR1c and β-Klotho, in particular human FGFR1c and human β-Klotho. Some of the agents, for example, are useful in mimicking the signaling effect generated in vivo by the association of FGFR1c with β-Klotho and with FGF21, and can thus be used to enhance or modulate one or more activities associated with FGF21-like signaling.

In general, the antigen binding proteins that are provided typically comprise one or more CDRs as described herein (e.g., 1, 2, 3, 4, 5 or 6 CDRs). In some embodiments the antigen binding proteins are naturally expressed by clones, while in other embodiments, the antigen binding protein can comprise (a) a polypeptide framework structure and (b) one or more CDRs that are inserted into and/or joined to the polypeptide framework structure. In some of these embodiments a CDR forms a component of a heavy or light chains expressed by the clones described herein; in other embodiments a CDR can be inserted into a framework in which the CDR is not naturally expressed. A polypeptide framework structure can take a variety of different forms. For example, a polypeptide framework structure can be, or comprise, the framework of a naturally occurring antibody, or fragment or variant thereof, or it can be completely synthetic in nature. Examples of various antigen binding protein structures are further described below.

In some embodiments in which the antigen binding protein comprises (a) a polypeptide framework structure and (b) one or more CDRs that are inserted into and/or joined to the polypeptide framework structure, the polypeptide framework structure of an antigen binding protein is an antibody or is derived from an antibody, including, but not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as "antibody mimetics"), chimeric antibodies, humanized antibodies, antibody fusions (sometimes referred to as "antibody conjugates"), and portions or fragments of each, respectively. In some instances, the antigen binding protein is an immunological fragment of an antibody (e.g., a Fab, a Fab', a $F(ab')_2$, or a scFv).

Certain of the antigen binding proteins as provided herein specifically bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, including the human forms of these proteins. In one embodiment, an antigen binding protein specifically binds to both human FGFR1c comprising the amino acid sequence of SEQ ID NO:5, and human β-Klotho comprising the amino acid sequence of SEQ ID NO:8, and in another embodiment an antigen binding protein specifically binds to both human FGFR1c comprising the amino acid sequence of SEQ ID NO:5 and human β-Klotho having the amino acid sequence of SEQ ID NO:8 and induces FGF21-like signaling. Thus, an antigen binding protein can, but need not, induce FGF21-like signaling.

Antigen Binding Protein Structure

Some of the antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, including the human forms of these proteins that are provided herein have a structure typically associated with naturally occurring antibodies. The structural units of these antibodies typically comprise one or more tetramers, each composed of two identical couplets of polypeptide chains, though some species of mammals also produce antibodies having only a single heavy chain. In a typical antibody, each pair or couplet includes one full-length "light" chain (in certain embodiments, about 25 kDa) and one full-length "heavy" chain (in certain embodiments, about

50-70 kDa). Each individual immunoglobulin chain is composed of several "immunoglobulin domains," each consisting of roughly 90 to 110 amino acids and expressing a characteristic folding pattern. These domains are the basic units of which antibody polypeptides are composed. The amino-terminal portion of each chain typically includes a variable domain that is responsible for antigen recognition. The carboxy-terminal portion is more conserved evolutionarily than the other end of the chain and is referred to as the "constant region" or "C region". Human light chains generally are classified as kappa ("κ") and lambda ("λ") light chains, and each of these contains one variable domain and one constant domain. Heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon chains, and these define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subtypes, including, but not limited to, IgG1, IgG2, IgG3, and IgG4. IgM subtypes include IgM, and IgM2. IgA subtypes include IgA1 and IgA2. In humans, the IgA and IgD isotypes contain four heavy chains and four light chains; the IgG and IgE isotypes contain two heavy chains and two light chains; and the IgM isotype contains five heavy chains and five light chains. The heavy chain C region typically comprises one or more domains that can be responsible for effector function. The number of heavy chain constant region domains will depend on the isotype. IgG heavy chains, for example, each contain three C region domains known as C_H1, C_H2 and C_H3. The antibodies that are provided can have any of these isotypes and subtypes. In certain embodiments, an antigen binding protein that specifically binds one or more of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 is an antibody of the IgG1, IgG2, or IgG4 subtype.

In full-length light and heavy chains, the variable and constant regions are joined by a "J" region of about twelve or more amino acids, with the heavy chain also including a "D" region of about ten more amino acids. See, e.g., Fundamental Immunology, 2nd ed., Ch. 7 (Paul, W., ed.) 1989, New York: Raven Press (hereby incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair typically form the antigen binding site.

One example of an IgG2 heavy constant domain of an exemplary monoclonal antibody that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 has the amino acid sequence:

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                                         (SEQ ID NO: 9)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV

HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVER

KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP

EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYK

CKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK

GFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQG

NVFSCSVMHEALHNHYTQKSLSLSPGK.
```

One example of a kappa light constant domain of an exemplary monoclonal antibody that binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 has the amino acid sequence:

```
                                        (SEQ ID NO: 10)
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG

NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK

SFNRGEC.
```

One example of a lambda light constant domain of an exemplary monoclonal antibody that binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 has the amino acid sequence:

```
                                        (SEQ ID NO: 11)
GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVK

AGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKT

VAPTECS
```

Variable regions of immunoglobulin chains generally exhibit the same overall structure, comprising relatively conserved framework regions (FR) joined by three hypervariable regions, more often called "complementarity determining regions" or CDRs. The CDRs from the two chains of each heavy chain/light chain pair mentioned above typically are aligned by the framework regions to form a structure that binds specifically with a specific epitope on the target protein (e.g., (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4). From N-terminal to C-terminal, naturally-occurring light and heavy chain variable regions both typically conform with the following order of these elements: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. A numbering system has been devised for assigning numbers to amino acids that occupy positions in each of these domains. This numbering system is defined in Kabat Sequences of Proteins of Immunological Interest (1987 and 1991, NIH, Bethesda, Md.). As desired, the CDRs can also be redefined according an alternative nomenclature scheme, such as that of Chothia (see Chothia & Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia et al., 1989, *Nature* 342:878-883 or Honegger & Pluckthun, 2001, *J. Mol. Biol.* 309:657-670.

The various heavy chain and light chain variable regions of antigen binding proteins provided herein are depicted in Table 2. Each of these variable regions can be attached to the above heavy and light chain constant regions to form a complete antibody heavy and light chain, respectively. Further, each of the so-generated heavy and light chain sequences can be combined to form a complete antibody structure. It should be understood that the heavy chain and light chain variable regions provided herein can also be attached to other constant domains having different sequences than the exemplary sequences listed above.

Specific examples of some of the full length light and heavy chains of the antibodies that are provided and their corresponding amino acid sequences are summarized in Tables 1A and 1B. Table 1A shows exemplary light chain sequences, and Table 1B shows exemplary heavy chain sequences.

TABLE 1A

Exemplary Antibody Light Chain Sequences

SEQ ID NO:	Designation	Contained in Clone	Amino Acid Sequence
12	L1	17C3	SYVLTQPPSVSVAPGQTARITCGGNNIGSQSVHWYQ QKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATL TISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTV LGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADGSPVKAGVETTKPSKQSNNKYAASS YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
13	L2	22H5	SYVLTQPPSVSVAPGQTARITCGGNNIGSQSVHWY QQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTAT LTISRVEAGDEADYYCQVWDNTSDHVVFGGGTKL TVLGQPKANPTVTLFPPSSEELQANKATLVCLISDF YPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPT ECS
14	L3	16H7 24H11	SYVLTQPPSVSVAPGQTARITCGGNNIGSESVHWYQ QKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATL TISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLT VLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADGSPVKAGVETTKPSKQSNNKYAAS SYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
15	L4	18G1	EIVLTQSPGTLSLSPGERATLSCRASQNFDSSYLAWY QQKPGQAPRLLIYGTSSRATGIPDRFSGIGSGTDFTLT INRLEPEDFAMYYCQQYGGSPLTFGGGTEVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
16	L5	17D8	EIVLTQSPGTLSLSPGERATLSCRASQSVSGNYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQYGSAPLTFGGGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
17	L6	26H11	EIVLTQSPGTLSLSPGERATLSCRASQSVSGNYLAW YQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDF TLTISRLEPEDFAMYYCQQYGSSPLTFGGGSKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
18	L7	12E4	EIVLTQSPGTLSLSPGERATLSCRASQNFDSNYLAWY QQKPGQAPRLLIYGASSRATGIPDNFSGSGSGTDFTL TISRLEPEDFAMYYCQQYGSSPLTFGGGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
19	L8	12C11	EIVLTQSPGTLSLSPGERATLSCRASQNFDSSSLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAMYYCQQCGSSPLTFGGGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
20	L9	21H2 21B4	EIVLTQSPGTLSLSPGERATLSCRASQSVSSTYLAWH QQKPGQGLRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQYGSSFTFGGGTRVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
21	L10	18B11.1	DIVMTQSPLSLPVTPGEPASISCRSSQSLLYYNGFTYL DWFLQKPGQSPHLLIYLGSNRASGVPDRFSGSVSGT DFTLKISRVEAEDVGVYYCMQSLQTPFTFGPGTKVD IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
22	L11	18B11.2	EIVMTQSPATLSVSPGERATLSCRASQSVNSNLAWY QQKPGQAPRLLIYGVSTRATGIPARFSGSGSGTEFTL TIRSLQSEDFAVYYCQQYNNWPPTFGQGTKVEIKRT

TABLE 1A-continued

Exemplary Antibody Light Chain Sequences			
SEQ ID NO:	Designation	Contained in Clone	Amino Acid Sequence
			VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
23	L12	20D4	DIQLTQSPSSLSASIGDRVTITCRASQDIRYDLGWYQ QKPGKAPKRLIYAASSLQSGVPSRFSGSGSGTEFTLT VSSLQPEDFATYYCLQHNSYPLTFGGGTKVEIERTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
24	L13	46D11	DIQMTQSPSSVSASVGDRVTITCRASQGISIWLAWYQ QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQANDFPITFGQGTRLEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC
25	L14	40D2	DFVMTQTPLSLSVTPGQPASISCKSSQSLLQSDGKTY LYWYLQKPGQPPHLLIYEVSNRFSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCMQSIQLPRTFGQGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
26	L15	37D3	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNFL DWYLQKPGQSPQLLIYLGSDRASGVPDRFSGSGSGT EFTLKISRVEAEDVGLYYCMQALQTPCSFGQGTKLE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
27	L16	39F7	EIVLTQSPGTLSLSPGERATLSCRASQSVSSTYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQSGSSPLTFGGGTEVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
28	L17	39F11	EIVLTQSPGTLSLSPGERATLSCRASQSVSSTYLAWY QQKPGQAPSLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQSGSSPLTFGGGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
29	L18	39G5	EIVLTQSPGTLSLSPGERATLSCRASQSVSSTYLAWY QQKPGQAPRLLIYGASFRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQSGSSPLTFGGGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

TABLE 1B

Exemplary Antibody Heavy Chain Sequences			
SEQ ID NO:	Designation	Contained in Clone	Sequence
30	H1	17C3	QVTLKESGPVLVKPTETLTLTCTVSGFSLSNARMG VSWIRQPPGKALEWLAHIFSNDEKSYSTSLKSRLTI SKDTSKSQVVLTMTNMDPVDTATYYCARILLLGA YYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVH QDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE

TABLE 1B-continued

Exemplary Antibody Heavy Chain Sequences

SEQ ID NO:	Designation	Contained in Clone	Sequence
			PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
31	H2	22H5	QVTLKESGPVLVKPTETLTLTCTVSGFSLSNARMG VSWIRQPPGKALEWLAHIFSNDEKSYSTSLKSRLTI SKDTSKSQVVLTMTNMDPVDTATYYCARILLVGA YYYCGMDVWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVH QDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
32	H3	16H7	QVTLKESGPVLVKPTETLTLTCTVSGFSLNNARMG VSWIRQPPGKALEWLAHIFSNDEKSYSTSLKSRLTI SKDTSKSQVVLIMTNMDPVDTATYYCARSVVTGG YYYDGMDVWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVH QDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
33	H4	24H11	QVTLKESGPVLVKPTETLTLTCTVSGFSLSNARMG VSWIRQPPGKALEWLAHIFSNDEKSYSTSLKNRLTI SKDTSKSQVVLIMTNMDPVDTATYYCARSVVTGG YYYDGMDVWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVH QDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
34	H5	18G1	EVQLLESGGGLVQPGGSLRLSCAASRFTFSTYAMS WVRQAPGKGLEWVSGISGSGVSTHYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLIVVI VYALDHWGQGTLVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHK PSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDW LNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
35	H6	17D8	EVQLLESGGGLVQPGGYLRLSCAASGFTFSTYAMS WVRQAPGKGLEWVSAISGSGVSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLIVV MVYVLDYWGQGTLVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVD HKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQ DWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

TABLE 1B-continued

Exemplary Antibody Heavy Chain Sequences			
SEQ ID NO:	Designation	Contained in Clone	Sequence
36	H7	26H11	EVQLLESGGGLVQPGGYLRLSCAASGFTFSTYAMS WVRQAPGKGLEWVSAISGSGVSTNYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLIVV MVYVLDYWGQGTLVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVD HKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQ DWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
37	H8	12E4 12C11	EVQLLESGGGLVQPGGSLRLSCAASRFTFSTYAMS WVRQAPGKGLEWVSGISGSGVSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLIVVI VYALDYWGQGTLVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHK PSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDW LNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
38	H9	21H2	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWS WIRQPAGKGLEWIGRIYTSGSTNYNPSLKSRVTMS KDTSKNQFSLKLRSVTAADTAVYYCARDPDGDYY YYGMDVWGQGTSVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDH KPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQD WLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
39	H10	21B4	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYFWS WIRQPAGKGLEWIGRIYTSGSTNYNPSLKSRVTMSI DTSKNQFSLKLSSVTAADTAVYYCARDPDGDYYY YGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTS ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKP SNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDW LNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
40	H11	18B11.1 18B11.2	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDAWM SWVRQAPGKGLEWVGRIKSKTDGGTTDYAAPVK GRFTISRDDSKNTLYLQMNSLKTEDTAVYFCTSTY SSGWYVWDYYGMDVWGQGTTVTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGT QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAP PVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVV SVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISK TKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
41	H12	20D4	QVQLVQSGAEVKKPGASVKVSCKVSGYTLTDLSM HWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRI TMTEDTSTDTAYMELSSLRSEDTAVYYCASIVVVP

TABLE 1B-continued

Exemplary Antibody Heavy Chain Sequences

SEQ ID NO:	Designation	Contained in Clone	Sequence
			AAIQSYYYYYGMGVWGQGTTVTVSSASTKGPSVF PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPV AGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSV LTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
42	H13	46D11	QVTLKEAGPVLVKPTETLTLTCTVSGFSLSNARMG VNWIRQPPGKALEWLAHIFSNDEKSYSTSLKSRLTI SKDTSKSQVVLTMTNMDPVDTATYYCARVRIAGD YYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPC SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCN VDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV HQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
43	H14	39F11	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGIH WVRQAPGKGLEWVAVIWYDGSDKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRA AAGLHYYYGMDVWGQGTTVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTY TCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVA GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVL TVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
44	H15	39F7	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGIH WVRQAPGKGLEWVAVIWYDGSIKYYADSVKGRF TISRDNSKNTLYLQMNSLRAEDTAVYYCARDRAA AGLHYYYGMDVWGQGTTVTVSSASTKGPSVFPL APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYT CNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
45	H16	39G5	QVQLVESGGGVVQPGRSLRLSCAVSGFTFSSYGIH WVRQAPGKGLEWVAVIWYDGSDKYYGDSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRA AAGLHYYYGMDVWGQGTTVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTY TCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVA GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVL TVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
46	H17	40D2	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYN WSWIRQHPGKGLEWIGNIYYSGSTYYNPSLKSRVT ISVDTSKNQFSLKLRSVTAADTAVYYCARENIVVIP AAIFAGWFDPWGQGTLVTVSSASTKGPSVFPLAPC

TABLE 1B-continued

Exemplary Antibody Heavy Chain Sequences

SEQ ID NO:	Designation	Contained in Clone	Sequence
			SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCN VDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV HQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
47	H18	37D3	EVHLVESGGGLAKPGGSLRLSCAASGFTFRNAWM SWVRQAPGKGLEWVGRIKSKTDGGTTDYAAPVK GRFTISRDDSKNTLYLQMNSLKTEDTAEYYCITDR VLSYYAMAVWGQGTTVTVSSASTKGPSVFPLAPC SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCN VDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV HQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Again, each of the exemplary heavy chains (H1, H2, H3 etc.) listed in Table 1B and 6A, infra, can be combined with any of the exemplary light chains shown in Table 1A and 6A, infra, to form an antibody. Examples of such combinations include H1 combined with any of L1 through L18; H2 combined with any of L1 through L18; H3 combined with any of L1 through L18, and so on. In some instances, the antibodies include at least one heavy chain and one light chain from those listed in Tables 1A and 1B and 6A, infra; particular examples pairings of light chains and heavy chains include L1 with H1, L2 with H2, L3 with H3, L4 with H4, L5 with H5, L6 with H6, L7 with H7, L8 with H8, L9 with H9, L10 with H10, L11 with H11, L12 with H12, L13 with H13, L14 with H14, L15 with H15, L16 with H16, L17 with H17, and L18 with H18. In addition to antigen binding proteins comprising a heavy and a light chain from the same clone, a heavy chain from a first clone can be paired with a light chain from a second clone (e.g., a heavy chain from 46D11 paired with a light chain from 16H7 or a heavy chain from 16H7 paired with a light chain from 46D11). Generally, such pairings can include VL with 90% or greater homology can be paired with the heavy chain of the naturally occurring clone. In some instances, the antibodies comprise two different heavy chains and two different light chains listed in Tables 1A and 1B and 6A, infra. In other instances, the antibodies contain two identical light chains and two identical heavy chains. As an example, an antibody or immunologically functional fragment can include two H1 heavy chains and two L1 light chains, or two H2 heavy chains and two L2 light chains, or two H3 heavy chains and two L3 light chains and other similar combinations of pairs of light chains and pairs of heavy chains as listed in Tables 1A and 1B and 6A, infra.

In another aspect of the instant disclosure, "hemibodies" are provided. A hemibody is a monovalent antigen binding protein comprising (i) an intact light chain, and (ii) a heavy chain fused to an Fc region (e.g., an IgG2 Fc region of SEQ ID NO:441), optionally via a linker, The linker can be a $(G_4S)_x$ linker where "x" is a non-zero integer (e.g., $(G_4S)_8$; SEQ ID NO:440). Hemibodies can be constructed using the provided heavy and light chain components. Specific examples of hemibodies are disclosed in Example 14.

Other antigen binding proteins that are provided are variants of antibodies formed by combination of the heavy and light chains shown in Tables 1A and 1B and 6A, infra and comprise light and/or heavy chains that each have at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to the amino acid sequences of these chains. In some instances, such antibodies include at least one heavy chain and one light chain, whereas in other instances the variant forms contain two identical light chains and two identical heavy chains.

Variable Domains of Antigen Binding Proteins

Also provided are antigen binding proteins that contain an antibody heavy chain variable region selected from the group consisting of V_H1, V_H2, V_H3, V_H4, V_H5, V_H6, V_H7, V_H8, V_H9, V_H10, V_H11, V_H12, V_H13, V_H14, V_H15, V_H16, V_H17 and V_H18 as shown in Table 2B and/or an antibody light chain variable region selected from the group consisting of V_L1, V_L2, V_L3, V_L4, V_L5, V_L6, V_L7, V_L8, V_L9, V_L10, V_L11, V_L12, V_L13, V_L14, V_L15, V_L16, V_L17 and V_L18 as shown in Table 2A, and immunologically functional fragments, derivatives, muteins and variants of these light chain and heavy chain variable regions.

TABLE 2A

Exemplary Antibody Variable Light (V_L) Chains

Contained in Clone	Designation	SEQ ID NO.	Amino Acid Sequence
17C3	V_L1	48	SYVLTQPPSVSVAPGQTARITCGGNNIGSQSVHWY QQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTA

TABLE 2A-continued

Exemplary Antibody Variable Light (V_L) Chains

Contained in Clone	Designation	SEQ ID NO.	Amino Acid Sequence
			TLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTK LTVL
22H5	V_L2	49	SYVLTQPPSVSVAPGQTARITCGGNNIGSQSVHWY QQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTA TLTISRVEAGDEADYYCQVWDNTSDHVVFGGGTK LTVL
16H7 24H11	V_L3	50	SYVLTQPPSVSVAPGQTARITCGGNNIGSESVHWY QQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTA TLTISRVEAGDEADYYCQVWDGNSDHVVFGGGT KLTVL
18G1	V_L4	51	EIVLTQSPGTLSLSPGERATLSCRASQNFDSSYLAW YQQKPGQAPRLLIYGTSSRATGIPDRFSGIGSGTDF TLTINRLEPEDFAMYYCQQYGGSPLTFGGGTEVEIK
17D8	V_L5	52	EIVLTQSPGTLSLSPGERATLSCRASQSVSGNYLA WYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGT DFTLTISRLEPEDFAVYYCQQYGSAPLTFGGGTKV EIK
26H11	V_L6	53	EIVLTQSPGTLSLSPGERATLSCRASQSVSGNYLA WYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGT DFTLTISRLEPEDFAMYYCQQYGSSPLTFGGGSKV EIK
12E4	V_L7	54	EIVLTQSPGTLSLSPGERATLSCRASQNFDSNYLA WYQQKPGQAPRLLIYGASSRATGIPDNFSGSGSGT DFTLTISRLEPEDFAMYYCQQYGSSPLTFGGGTKV EIK
12C11	V_L8	55	EIVLTQSPGTLSLSPGERATLSCRASQNFDSSSLAW YQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDF TLTISRLEPEDFAMYYCQQCGSSPLTFGGGTKVEIK
21H2 21B4	V_L9	56	EIVLTQSPGTLSLSPGERATLSCRASQSVSSTYLAW HQQKPGQGLRLLIYGASSRATGIPDRFSGSGSGTDF TLTISRLEPEDFAVYYCQQYGSSFTFGGGTRVEIK
18B11.1	V_L10	57	DIVMTQSPLSLPVTPGEPASISCRSSQSLLYYNGFT YLDWFLQKPGQSPHLLIYLGSNRASGVPDRFSGSV SGTDFTLKISRVEAEDVGVYYCMQSLQTPFTFGPG TKVDIK
18B11.2	V_L11	58	EIVMTQSPATLSVSPGERATLSCRASQSVNSNLAW YQQKPGQAPRLLIYGVSTRATGIPARFSGSGSGTEF TLTIRSLQSEDFAVYYCQQYNNWPPTFGQGTKVEIK
20D4	V_L12	59	DIQLTQSPSSLSASIGDRVTITCRASQDIRYDLGWY QQKPGKAPKRLIYAASSLQSGVPSRFSGSGSGTEFT LTVSSLQPEDFATYYCLQHNSYPLTFGGGTKVEIE
46D11	V_L13	60	DIQMTQSPSSVSASVGDRVTITCRASQGISIWLAW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQANDFPITFGQGTRLEIK
40D2	V_L14	61	DFVMTQTPLSLSVTPGQPASISCKSSQSLLQSDGKT YLYWYLQKPGQPPHLLIYEVSNRFSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCMQSIQLPRTFGQG TKVEIK
37D3	V_L15	62	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYN FLDWYLQKPGQSPQLLIYLGSDRASGVPDRFSGSG SGTEFTLKISRVEAEDVGLYYCMQALQTPCSFGQG TKLEIK
39F7	V_L16	63	EIVLTQSPGTLSLSPGERATLSCRASQSVSSTYLAW YQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDF TLTISRLEPEDFAVYYCQQSGSSPLTFGGGTEVEIK
39F11	V_L17	64	EIVLTQSPGTLSLSPGERATLSCRASQSVSSTYLAW YQQKPGQAPSLLIYGASSRATGIPDRFSGSGSGTDF TLTISRLEPEDFAVYYCQQSGSSPLTFGGGTKVEIK

TABLE 2A-continued

Exemplary Antibody Variable Light (V_L) Chains			
Contained in Clone	Designation	SEQ ID NO.	Amino Acid Sequence
39G5	V_L18	65	EIVLTQSPGTLSLSPGERATLSCRASQSVSSTYLAW YQQKPGQAPRLLIYGASFRATGIPDRFSGSGSGTDF TLTISRLEPEDFAVYYCQQSGSSPLTFGGGTKVEIK

TABLE 2B

Exemplary Antibody Variable Heavy (V_H) Chains			
Contained in Clone	Designation	SEQ ID NO.	Amino Acid Sequence
17C3	V_H1	66	QVTLKESGPVLVKPTETLTLTCTVSGFSLSNARMG VSWIRQPPGKALEWLAHIFSNDEKSYSTSLKSRLTI SKDTSKSQVVLTMTNMDPVDTATYYCARILLLGA YYYYGMDVWGQGTTVTVSS
22H5	V_H2	67	QVTLKESGPVLVKPTETLTLTCTVSGFSLSNARMG VSWIRQPPGKALEWLAHIFSNDEKSYSTSLKSRLTI SKDTSKSQVVLTMTNMDPVDTATYYCARILLVGA YYYCGMDVWGQGTTVTVSS
16H7	V_H3	68	QVTLKESGPVLVKPTETLTLTCTVSGFSLNNARMG VSWIRQPPGKALEWLAHIFSNDEKSYSTSLKSRLTI SKDTSKSQVVLIMTNMDPVDTATYYCARSVVTGG YYYDGMDVWGQGTTVTVSS
24H11	V_H4	69	QVTLKESGPVLVKPTETLTLTCTVSGFSLSNARMG VSWIRQPPGKALEWLAHIFSNDEKSYSTSLKNRLTI SKDTSKSQVVLIMTNMDPVDTATYYCARSVVTGG YYYDGMDVWGQGTTVTVSS
18G1	V_H5	70	EVQLLESGGGLVQPGGSLRLSCAASRFTFSTYAMS WVRQAPGKGLEWVSGISGSGVSTHYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLIVVI VYALDHWGQGTLVTVSS
17D8	V_H6	71	EVQLLESGGGLVQPGGYLRLSCAASGFTFSTYAMS WVRQAPGKGLEWVSAISGSGVSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLIVV MVYVLDYWGQGTLVTVSS
26H11	V_H7	72	EVQLLESGGGLVQPGGYLRLSCAASGFTFSTYAMS WVRQAPGKGLEWVSAISGSGVSTNYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLIVV MVYVLDYWGQGTLVTVSS
12E4 12C11	V_H8	73	EVQLLESGGGLVQPGGSLRLSCAASRFTFSTYAMS WVRQAPGKGLEWVSGISGSGVSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLIVVI VYALDYWGQGTLVTVSS
21H2	V_H9	74	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWS WIRQPAGKGLEWIGRIYTSGSTNYNPSLKSRVTMS KDTSKNQFSLKLRSVTAADTAVYYCARDPDGDYY YYGMDVWGQGTSVTVSS
21B4	V_H10	75	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYFWS WIRQPAGKGLEWIGRIYTSGSTNYNPSLKSRVTMS IDTSKNQFSLKLSSVTAADTAVYYCARDPDGDYY YYGMDVWGQGTTVTVSS
18B11.1	V_H11	76	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDAWM SWVRQAPGKGLEWVGRIKSKTDGGTTDYAAPVK GRFTISRDDSKNTLYLQMNSLKTEDTAVYFCTSTY SSGWYVWDYYGMDVWGQGTTVTVSS
18B11.2	V_H11	77	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDAWM SWVRQAPGKGLEWVGRIKSKTDGGTTDYAAPVK GRFTISRDDSKNTLYLQMNSLKTEDTAVYFCTSTY SSGWYVWDYYGMDVWGQGTTVTVSS

TABLE 2B-continued

Exemplary Antibody Variable Heavy (V_H) Chains			
Contained in Clone	Designation	SEQ ID NO.	Amino Acid Sequence
20D4	V_H12	78	QVQLVQSGAEVKKPGASVKVSCKVSGYTLTDLSM HWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGR ITMTEDTSTDTAYMELSSLRSEDTAVYYCASIVVV PAAIQSYYYYYGMGVWGQGTTVTVSS
46D11	V_H13	79	QVTLKEAGPVLVKPTETLTLTCTVSGFSLSNARMG VNWIRQPPGKALEWLAHIFSNDEKSYSTSLKSRLTI SKDTSKSQVVLTMTNMDPVDTATYYCARVRIAGD YYYYYGMDVWGQGTTVTVSS
40D2	V_H14	80	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYN WSWIRQHPGKGLEWIGNIYYSGSTYYNPSLKSRVT ISVDTSKNQFSLKLRSVTAADTAVYYCARENIVVIP AAIFAGWFDPWGQGTLVTVSS
37D3	V_H15	81	EVHLVESGGGLAKPGGSLRLSCAASGFTFRNAWM SWVRQAPGKGLEWVGRIKSKTDGGTTDYAAPVK GRFTISRDDSKNTLYLQMNSLKTEDTAEYYCITDR VLSYYAMAVWGQGTTVTVSS
39F7	V_H16	82	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGIH WVRQAPGKGLEWVAVIWYDGSIKYYADSVKGRF TISRDNSKNTLYLQMNSLRAEDTAVYYCARDRAA AGLHYYYGMDVWGQGTTVTVSS
39F11	V_H17	83	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGIH WVRQAPGKGLEWVAVIWYDGSDKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRA AAGLHYYYGMDVWGQGTTVTVSS
39G5	V_H18	84	QVQLVESGGGVVQPGRSLRLSCAVSGFTFSSYGIH WVRQAPGKGLEWVAVIWYDGSDKYYGDSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRA AAGLHYYYGMDVWGQGTTVTVSS

TABLE 2C

Coding Sequence for Antibody Variable Light (V_L) Chains			
Contained in Clone	Designation	SEQ ID NO.	Coding Sequence
17C3	V_L1	85	TCCTATGTGCTGACTCAGCCACCCTCGGTGTCAG TGGCCCCAGGTCAGACGGCCAGGATTACCTGTG GGGGAAACAACATTGGAAGTCAGAGTGTGCACT GGTACCAGCAGAAGCCAGGCCAGGCCCCTGTCC TGGTCGTCTATGATGATAGCGACCGGCCCTCAG GGATCCCTGAGCGATTCTCTGGCTCCAACTCTGG GAACACGGCCACCCTGACCATCAGCAGGGTCGA AGCCGGGGATGAGGCCGACTATTACTGTCAGGT GTGGGATAGTAGTAGTGATCATGTGGTATTCGG CGGAGGGACCAAGCTGACCGTCCTA
22H5	V_L2	86	TCCTATGTGCTGACTCAGCCACCCTCGGTGTCAG TGGCCCCAGGACAGACGGCCAGGATTACCTGTG GGGGAAACAACATTGGAAGTCAAAGTGTGCACT GGTACCAGCAGAAGCCAGGCCAGGCCCCTGTCC TGGTCGTCTATGATGATAGCGACCGGCCCTCAG GGATCCCTGAGCGATTCTCTGGCTCCAACTCTGG GAACACGGCCACCCTGACCATCAGCAGGGTCGA AGCCGGGGATGAGGCCGACTATTACTGTCAGGT GTGGGATAATACTAGTGATCATGTGGTATTCGG CGGGGGGACCAAACTGACCGTCCTA
16H7 24H11	V_L3	87	TCCTATGTGCTGACTCAGCCACCCTCGGTGTCAG TGGCCCCAGGACAGACGGCCAGGATTACCTGTG GGGGAAACAACATTGGAAGTGAAAGTGTGCACT GGTACCAGCAGAAGCCAGGCCAGGCCCCTGTGC TGGTCGTCTATGATGATAGCGACCGGCCCTCAG GGATCCCTGAGCGATTCTCTGGCTCCAACTCTGG GAACACGGCCACCCTGACCATCAGCAGGGTCGA

TABLE 2C-continued

Coding Sequence for Antibody Variable Light (V_L) Chains			
Contained in Clone	Designation	SEQ ID NO.	Coding Sequence
			AGCCGGGGATGAGGCCGACTATTACTGTCAGGT GTGGGATGGTAATAGTGATCATGTGGTATTCGG CGGAGGGACCAAGCTGACCGTCCTA
18G1	V_LA	88	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTG TCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCT GCAGGGCCAGTCAGAATTTTGACAGCAGTTACT TAGCCTGGTACCAGCAGAAACCTGGCCAGGCTC CCCGGCTCCTCATCTATGGTACATCCAGCAGGG CCACTGGCATCCCAGACAGGTTCAGTGGCATTG GGTCTGGGACAGACTTCACTCTCACCATCAACA GACTGGAGCCTGAAGATTTTGCAATGTATTACT GTCAGCAGTATGGTGGCTCACCGCTCACTTTCGG CGGAGGGACCGAGGTGGAAATCAAA
17D8	V_L5	89	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTG TCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCT GCAGGGCCAGTCAGAGTGTTAGCGGCAACTACT TGGCCTGGTACCAGCAGAAACCTGGCCAGGCTC CCAGGCTCCTCATCTATGGTGCATCCAGCAGGG CCACTGGCATCCCAGACAGGTTCAGTGGCAGTG GGTCTGGGACAGACTTCACTCTCACCATCAGCA GACTGGAGCCTGAAGATTTTGCAGTGTATTATTG TCAGCAGTATGGTAGCGCACCGCTCACTTTCGG CGGAGGGACCAAGGTGGAAATCAAA
26H11	V_L6	90	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTG TCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCT GCAGGGCCAGTCAGAGTGTTAGCGGCAACTACT TGGCCTGGTACCAGCAGAAACCTGGCCAGGCTC CCAGGCTCCTCATCTATGGTGCATCCAGCAGGG CCACTGGCATCCCAGACAGATTCAGTGGCAGTG GGTCTGGGACAGACTTCACTCTCACCATCAGCA GACTGGAGCCTGAAGATTTTGCAATGTATTATTG TCAGCAGTATGGTAGCTCACCGCTCACTTTCGGC GGAGGGTCCAAGGTGGAGATCAAA
12E4	V_L7	91	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTG TCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCT GCAGGGCCAGTCAGAATTTCGACAGCAACTACT TAGCCTGGTACCAGCAGAAGCCTGGCCAGGCTC CCCGGCTCCTCATCTATGGTGCATCCAGCAGGG CCACTGGCATCCCAGACAACTTCAGTGGCAGTG GGTCTGGGACAGACTTCACTCTCACCATCAGCA GACTGGAGCCTGAAGATTTTGCAATGTATTACT GTCAGCAGTATGGTAGTTCACCGCTCACTTTCGG CGGAGGGACCAAGGTGGAAATCAAA
12C11	V_L8	92	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTG TCTTTGTCTCCAGGGGAAAGGGCCACCCTCTCCT GCAGGGCCAGTCAGAATTTTGACAGCAGCTCCT TAGCCTGGTACCAGCAGAAACCTGGCCAGGCTC CCCGGCTCCTCATCTATGGTGCATCCAGCAGGG CCACTGGCATCCCAGACAGGTTCAGTGGCAGTG GGTCTGGGACAGACTTCACTCTCACCATCAGCA GACTGGAGCCTGAAGATTTTGCAATGTATTACT GTCAGCAGTGTGGTAGCTCACCGCTCACTTTCGG CGGAGGGACCAAGGTGGAAATCAAA
21H2 21B4	V_L9	93	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTG TCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCT GCAGGGCCAGTCAGAGTGTTAGCAGTACCTACT TAGCCTGGCACCAGCAGAAACCTGGCCAGGGTC TTAGGCTCCTCATCTATGGTGCATCCAGCAGGGC CACTGGCATCCCAGACAGGTTCAGTGGCAGTGG GTCTGGGACAGACTTCACTCTTACCATCAGCAG ACTGGAGCCTGAAGATTTTGCAGTGTATTACTGT CAGCAGTATGGAAGCTCATTCACTTTCGGCGGA GGGACCAGGGTGGAGATCAAA
18B11.1	V_L10	94	GATATTGTGATGACTCAGTCTCCACTCTCCCTGC CCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTG CAGGTCTAGTCAGAGCCTCCTGTATTATAATGG ATTCACCTATTTGGATTGGTTCCTGCAGAAGCCA GGGCAGTCTCCACATCTCCTGATCTATTTGGGTT

TABLE 2C-continued

Coding Sequence for Antibody Variable Light (V_L) Chains

Contained in Clone	Designation	SEQ ID NO.	Coding Sequence
			CTAATCGGGCCTCCGGGGTCCCTGACAGGTTCA GTGGCAGTGTTTCAGGCACAGATTTTACACTGA AAATCAGCAGAGTGGAGGCTGAGGATGTTGGGG TTTATTATTGCATGCAGTCTCTGCAAACTCCATT CACTTTCGGCCCTGGGACCAAAGTGGATATCAAA
18B11.2	V_L11	95	GAAATAGTGATGACGCAGTCTCCAGCCACCCTG TCTGTGTCTCCAGGGGAAAGAGCCACCCTCTCCT GCAGGGCCAGTCAGAGTGTTAACAGCAACTTAG CCTGGTACCAGCAGAAACCTGGCCAGGCTCCCA GGCTCCTCATTTATGGTGTATCCACCAGGGCCAC TGGTATCCCAGCCAGGTTCAGTGGCAGTGGGTC TGGGACAGAGTTCACTCTCACCATCCGCAGCCT GCAGTCTGAAGATTTTGCAGTTTATTACTGTCAG CAGTATAATAACTGGCCTCCGACGTTCGGCCAA GGGACCAAGGTGGAAATCAAA
20D4	V_L12	96	GACATACAGCTGACCCAGTCTCCATCCTCCCTGT CTGCATCTATAGGAGACAGAGTCACCATCACTT GCCGGGCAAGTCAGGACATTAGATATGATTTAG GCTGGTATCAGCAGAAACCAGGGAAAGCCCCTA AGCGCCTGATCTATGCTGCATCCAGTTTGCAAA GTGGGGTCCCTTCAAGGTTCAGCGGCAGTGGAT CTGGGACAGAATTCACTCTCACAGTCAGCAGCC TGCAGCCTGAAGATTTTGCAACTTATTACTGTCT ACAGCATAATAGTTACCCTCTCACTTTCGGCGGA GGGACCAAGGTGGAGATCGAA
46D11	V_L13	97	GACATCCAGATGACCCAGTCTCCCTCTTCCGTGT CTGCATCTGTAGGAGACAGAGTCACCATCACTT GTCGGGCGAGTCAGGGTATTAGCATCTGGTTAG CCTGGTATCAGCAGAAACCTGGGAAAGCCCCTA AACTCCTGATCTATGCTGCATCCAGTTTGCAAAG TGGGGTCCCATCAAGGTTCAGCGGCAGTGGATC TGGGACAGATTTCACTCTCACCATCAGCAGCCT GCAGCCTGAAGATTTTGCAACTTACTATTGTCAA CAGGCTAACGATTTCCCGATCACCTTCGGCCAA GGGACACGACTGGAGATTAAA
40D2	V_L14	98	GATTTTGTGATGACCCAGACTCCACTCTCTCTGT CCGTCACCCCTGGACAGCCGGCCTCCATCTCCTG CAAGTCTAGTCAGAGCCTCCTACAGAGTGATGG AAAGACCTATTTGTATTGGTACCTGCAGAAGCC AGGCCAGCCTCCACATCTCCTGATCTATGAAGTT TCCAACCGATTCTCTGGAGTGCCAGATAGGTTC AGTGGCAGCGGGTCAGGGACAGATTTCACACTG AAAATCAGCCGGGTGGAGGCTGAGGATGTTGGG GTTTATTACTGCATGCAAAGTATACAGCTTCCTC GGACGTTCGGCCAAGGGACCAAGGTGGAAATCA AA
37D3	V_L15	99	GATATTGTGATGACTCAGTCTCCACTCTCCCTGC CCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTG CAGGTCTAGTCAGAGCCTCCTGCATAGTAATGG ATACAACTTTTTGGATTGGTACCTACAGAAGCC AGGGCAGTCTCCACAGCTCCTGATCTATTTGGGT TCTGATCGGGCCTCCGGGGTCCCTGACAGGTTC AGTGGCAGTGGATCAGGCACAGAGTTTACACTG AAAATCAGCAGAGTGGAGGCTGAGGATGTTGGG CTTTATTACTGCATGCAAGCTCTACAAACTCCGT GCAGTTTTGGCCAGGGGACCAAGCTGGAGATCA AA
39F7	V_L16	100	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTG TCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCT GCAGGGCCAGTCAGAGTGTTAGTAGCACCTATT TAGCCTGGTACCAGCAGAAACCTGGCCAGGCTC CCAGGCTCCTCATCTATGGTGCATCCAGCAGGG CCACTGGCATCCCAGACAGGTTCAGTGGCAGTG GGTCTGGGACAGACTTCACTCTCACCATCAGCA GACTGGAGCCTGAAGATTTTGCAGTTTATTACTG TCAGCAGTCTGGTAGCTCACCGCTCACTTTCGGC GGAGGGACCGAGGTGGAGATCAAA

TABLE 2C-continued

Coding Sequence for Antibody Variable Light (V_L) Chains

Contained in Clone	Designation	SEQ ID NO.	Coding Sequence
39F11	V_L17	101	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTG TCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCT GCAGGGCCAGTCAGAGTGTTAGCAGCACCTACT TAGCCTGGTACCAGCAGAAACCTGGCCAGGCTC CCAGTCTCCTCATCTATGGTGCATCCAGCAGGGC CACTGGCATCCCAGACAGGTTCAGTGGCAGTGG GTCTGGGACAGACTTCACTCTCACCATCAGCAG ACTGGAGCCTGAGGATTTTGCAGTGTATTACTGT CAGCAGTCTGGTAGCTCACCTCTCACTTTCGGCG GAGGGACCAAGGTGGAGATCAAA
30G5	V_L18	102	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTG TCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCT GCAGGGCCAGTCAGAGTGTTAGCAGCACCTACT TAGCCTGGTACCAGCAGAAACCTGGCCAGGCTC CCAGGCTCCTCATCTATGGTGCATCCTTCAGGGC CACTGGCATCCCAGACAGGTTCAGTGGCAGTGG GTCTGGGACAGACTTCACTCTCACCATCAGCAG ACTGGAGCCTGAGGATTTTGCAGTGTATTACTGT CAGCAGTCTGGTAGCTCACCTCTCACTTTCGGCG GAGGGACCAAGGTGGAGATCAAA

TABLE 2D

Coding Sequence for Antibody Variable Heavy (V_H) Chains

Contained in Clone	Designation	SEQ ID NO.	Coding Sequence
17C3	V_H1	103	CAGGTCACCTTGAAGGAGTCTGGTCCTGTGCTG GTGAAACCCACAGAGACCCTCACGCTGACCTGC ACCGTCTCTGGGTTCTCACTCAGCAATGCTAGAA TGGGTGTGAGCTGGATCCGTCAGCCCCCAGGGA AGGCCCTGGAGTGGCTTGCACACATTTTTTCGAA TGACGAAAAATCCTACAGCACATCTCTGAAGAG CAGGCTCACCATCTCCAAGGACACCTCCAAAAG CCAGGTGGTCCTTACCATGACCAACATGGACCC TGTGGACACAGCCACATATTACTGTGCACGGAT ATTATTACTGGGAGCTTACTACTACTACGGTATG GACGTCTGGGGCCAAGGGACCACGGTCACCGTC TCCTCA
22H5	V_H2	104	CAGGTCACCTTGAAGGAGTCTGGTCCTGTGCTG GTGAAACCCACAGAGACCCTCACGCTGACCTGC ACCGTCTCTGGGTTCTCACTCAGCAATGCTAGAA TGGGTGTGAGCTGGATCCGTCAGCCCCCAGGGA AGGCCCTGGAGTGGCTTGCACACATTTTTTCGAA TGACGAAAAATCCTACAGCACATCTCTGAAGAG CAGGCTCACCATCTCCAAGGACACCTCCAAAAG CCAGGTGGTCCTTACCATGACCAACATGGACCC TGTGGACACAGCCACATATTACTGTGCACGGAT ATTATTAGTGGGAGCTTACTACTACTGCGGTATG GACGTCTGGGGCCAAGGGACCACGGTCACCGTC TCCTCA
16H7	V_H3	105	CAGGTCACCTTGAAGGAGTCTGGTCCTGTGCTG GTGAAACCCACAGAGACCCTCACGCTGACCTGC ACCGTCTCTGGGTTCTCACTCAACAATGCTAGAA TGGGTGTGAGCTGGATCCGTCAGCCCCCAGGGA AGGCCCTGGAGTGGCTTGCACACATTTTTTCGAA TGACGAAAAATCCTACAGCACATCTCTGAAGAG CAGGCTCACCATCTCCAAGGACACCTCCAAAAG CCAGGTGGTCCTAATTATGACCAACATGGACCC TGTGGACACAGCCACATATTACTGTGCACGGTC AGTAGTAACTGGCGGCTACTACTACGACGGTAT GGACGTCTGGGGCCAAGGGACCACGGTCACCGT CTCCTCA
24H11	V_H4	106	CAGGTCACCTTGAAGGAGTCTGGTCCTGTGCTG GTGAAACCCACAGAGACCCTCACGCTGACCTGC ACCGTCTCTGGGTTCTCACTCAGCAATGCTAGAA

TABLE 2D-continued

Coding Sequence for Antibody Variable Heavy (V_H) Chains			
Contained in Clone	Designation	SEQ ID NO.	Coding Sequence
			TGGGTGTGAGCTGGATCCGTCAGCCCCCAGGGAAGGCCCTGGAGTGGCTTGCACACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAACAGGCTCACCATCTCCAAGGACACCTCCAAAAGCCAGGTGGTCCTTATTATGACCAACATGGACCCTGTGGACACAGCCACATATTACTGTGCACGGTCAGTAGTGACTGGCGGCTACTACTACGACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
18G1	V_H5	107	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGGTTGGTACAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTAGATTCACCTTTAGCACCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGGTATTAGTGGTAGTGGTGTCAGCACACACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAATCCCTCATTGTAGTAATAGTATATGCCCTTGACCACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA
17D8	V_H6	108	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTACCTGAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTACCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTCTCAGCTATCAGTGGTAGTGGTGTTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAATCCCTTATTGTAGTAATGGTGTATGTCCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA
26H11	V_H7	109	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTACCTGAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGCACCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTCTCAGCTATTAGTGGCAGTGGTGTGAGCACAAACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAATCCCTTATTGTAGTAATGGTGTATGTCCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA
12E4 12C11	V_H8	110	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGGTTGGTACAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTAGATTCACCTTTAGCACCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGGTATTAGTGGTAGTGGTGTTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAATCCCTTATTGTAGTAATAGTATATGCCCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA
21H2	V_H9	111	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTACTGGAGCTGGATCCGGCAGCCCGCCGGGAAGGGACTGGAGTGGATTGGGCGTATCTATACCAGTGGGAGCACCAACTACAACCCCTCCCTCAAGAGTCGGGTCACCATGTCAAAAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGGTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGATCCGGACGGTGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCTCGGTCACCGTCTCCTCA
21B4	V_H10	112	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTTCTGGAGCTGGATCCGGCAGCCCGCCGGGAAGGGACTGGAGTGGATTGGGCGTATCTATACCAGTGGG

TABLE 2D-continued

Coding Sequence for Antibody Variable Heavy (V_H) Chains

Contained in Clone	Designation	SEQ ID NO.	Coding Sequence
			AGCACCAACTACAACCCCTCCCTCAAGAGTCGA GTCACCATGTCAATAGACACGTCCAAGAACCAG TTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCGG ACACGGCCGTGTATTACTGTGCGAGAGATCCGG ACGGTGACTACTACTACTACGGTATGGACGTCT GGGGCCAAGGGACCACGGTCACCGTCTCCTCA
18B11.1 18B11.2	V_H11	113	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTG GTAAAGCCTGGGGGGTCCCTTAGACTCTCCTGT GCAGCCTCTGGATTCACTTTCAGTGACGCCTGGA TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGC TGGAGTGGGTTGGCCGTATTAAAAGCAAAACTG ATGGTGGGACAACAGACTACGCTGCACCCGTGA AAGGCAGATTCACCATCTCAAGAGATGATTCAA AAAACACTCTGTATCTGCAAATGAACAGCCTGA AAACCGAGGACACAGCCGTGTATTTTTGTACCT CTACGTATAGCAGTGGCTGGTACGTATGGGACT ACTACGGTATGGACGTCTGGGGCCAAGGGACCA CGGTCACCGTCTCCTCA
20D4	V_H12	114	CAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTG AAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGC AAGGTTTCGGGATACACCCTCACTGATTTATCCA TGCACTGGGTGCGACAGGCTCCTGGAAAAGGGC TTGAGTGGATGGGAGGTTTTGATCCTGAAGATG GTGAAACAATCTACGCACAGAAGTTCCAGGGCA GAATCACCATGACCGAGGACACATCTACAGACA CAGCCTACATGGAGCTGAGCAGCCTGAGATCTG AGGACACGGCCGTGTATTACTGTGCAAGTATTG TAGTAGTCCCAGCTGCTATACAGAGTTACTACTA CTACTACGGTATGGGCGTCTGGGGCCAAGGGAC CACGGTCACCGTCTCCTCC
46D11	V_H13	115	CAGGTCACCTTGAAGGAGGCTGGTCCTGTGTTG GTGAAACCCACAGAGACCCTCACGTTGACCTGC ACCGTCTCTGGGTTCTCACTCAGCAATGCTAGAA TGGGTGTGAACTGGATCCGTCAGCCCCCAGGGA AGGCCCTGGAGTGGCTTGCACACATTTTTTCGAA TGACGAAAAATCCTACAGCACATCTCTGAAGAG CAGGCTCACCATCTCCAAGGACACCTCCAAAAG CCAGGTGGTCCTTACCATGACCAACATGGACCC TGTGGACACAGCCACATATTACTGTGCACGGGT TCGTATAGCAGGTGATTACTACTACTACTACGGT ATGGACGTCTGGGGCCAAGGGACCACGGTCACC GTCTCCTCA
40D2	V_H14	116	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTG GTGAAGCCTTCACAGACCCTGTCCCTCACCTGCA CTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTTA CAACTGGAGCTGGATCCGCCAGCACCCAGGGAA GGGCCTGGAGTGGATTGGGAACATCTATTACAG TGGGAGCACCTACTACAACCCGTCCCTCAAGAG TCGAGTTACCATATCAGTAGACACGTCTAAGAA CCAGTTCTCCCTGAAGCTGAGATCTGTGACTGCC GCGGACACGGCCGTGTATTACTGTGCGAGAGAG AATATTGTAGTAATACCAGCTGCTATATTCGCGG GTTGGTTCGACCCCTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
37D3	V_H15	117	GAGGTGCACCTGGTGGAGTCTGGGGGAGGCTTG GCAAAGCCTGGGGGGTCCCTTAGACTCTCCTGT GCAGCCTCTGGATTCACTTTCAGAAACGCCTGG ATGAGCTGGGTCCGCCAGGCTCCAGGAAAGGGG CTGGAATGGGTTGGCCGTATTAAAAGCAAAACT GATGGTGGGACAACAGACTACGCTGCACCCGTG AAAGGCAGATTCACCATCTCGAGAGATGATTCA AAAAACACGCTGTATCTGCAAATGAACAGCCTG AAAACCGAGGACACAGCCGAGTATTACTGTATC ACAGATCGGGTGCTAAGCTACTACGCTATGGCC GTCTGGGGCCAAGGGACCACGGTCACCGTCTCC TCA
39F7	V_H16	118	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTG GTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGT GCAGCGTCTGGATTCACCTTCAGTAACTATGGC

TABLE 2D-continued

Coding Sequence for Antibody Variable Heavy (V_H) Chains

Contained in Clone	Designation	SEQ ID NO.	Coding Sequence
			ATTCACTGGGTCCGCCAGGCTCCAGGCAAGGGG CTGGAGTGGGTGGCAGTTATATGGTATGATGGA AGTATTAAATACTATGCAGACTCCGTGAAGGGC CGATTCACCATCTCCAGAGACAATTCCAAGAAC ACGCTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCTGTGTATTACTGTGCGAGAGAT AGGGCAGCAGCTGGTCTCCACTACTACTACGGT ATGGACGTCTGGGGCCAAGGGACCACGGTCACC GTCTCCTCA
39F11	V_H17	119	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTG GTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGT GCAGCGTCTGGATTCACCTTCAGTAGCTATGGC ATCCACTGGGTCCGCCAGGCTCCAGGCAAGGGG CTGGAATGGGTGGCAGTTATATGGTATGATGGA AGTGATAAATACTATGCAGACTCCGTGAAGGGC CGATTCACCATCTCCAGAGACAATTCCAAGAAC ACGCTGTATCTACAAATGAACAGCCTGAGAGCC GAGGACACGGCTGTGTATTACTGTGCGAGAGAT AGGGCAGCAGCTGGTCTCCACTATTATTACGGT ATGGACGTCTGGGGCCAAGGGACCACGGTCACC GTCTCCTCA
39G5	V_H18	120	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTG GTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGT GCAGTGTCTGGATTCACCTTCAGTAGCTATGGCA TCCACTGGGTCCGCCAGGCTCCAGGCAAGGGGC TGGAATGGGTGGCAGTTATATGGTATGATGGAA GTGATAAATACTATGGAGACTCCGTGAAGGGCC GATTCACCATCTCCAGAGACAATTCCAAGAACA CGCTGTATCTACAAATGAACAGCCTGAGAGCCG AGGACACGGCTGTGTATTACTGTGCGAGAGATA GGGCAGCAGCTGGTCTCCACTATTATTACGGTAT GGACGTCTGGGGCCAAGGGACCACGGTCACCGT CTCCTCA

Each of the heavy chain variable regions listed in Table 2B can be combined with any of the light chain variable regions shown in Table 2A to form an antigen binding protein. Examples of such combinations include V_H1 combined with any of V_L1, V_L2, V_L3, V_L4, V_L5, V_L6, V_L7, V_L8, V_L9, V_L10, V_L11, V_L12, V_L13, V_L14, V_L15, V_L16, V_L17 or V_L18; V_H2 combined with any of V_L1, V_L2, V_L3, V_L4, V_L5, V_L6, V_L7, V_L8, V_L9, V_L10, V_L11, V_L12, V_L13, V_L14, V_L15, V_L16, V_L17 or V_L18; V_H3 combined with any of V_L1, V_L2, V_L3, V_L4, V_L5, V_L6, V_L7, V_L8, V_L9, V_L10, V_L11, V_L12, V_L13, V_L14, V_L15, V_L16, V_L17 or V_L18; and so on.

In some instances, the antigen binding protein includes at least one heavy chain variable region and/or one light chain variable region from those listed in Tables 2A and 2B. In some instances, the antigen binding protein includes at least two different heavy chain variable regions and/or light chain variable regions from those listed in Table 2B. An example of such an antigen binding protein comprises (a) one V_H1, and (b) one of V_H2, V_H3, V_H4, V_H5, V_H6, V_H7, V_H8, V_H9, V_H10, V_H11, V_H12, VH_{13}, VH_{14}, VH_{15}, VH_{16}, VH_{17} or VH_{18}. Another example comprises (a) one V_H2, and (b) one of V_H1, V_H3, V_H4, V_H5, V_H6, V_H7, V_H8, V_H9, V_H10, V_H11, V_H12, V_H13, V_H14, V_H15, V_H16, V_H17 or V_H18. Again another example comprises (a) one V_H3, and (b) one of V_H1, V_H2, V_H4, V_H5, V_H6, V_H7, V_H8, V_H9, V_H10, V_H11, V_H12, V_H13, V_H14, V_H15 V_H16, V_H17 or V_H18, etc.

Again another example of such an antigen binding protein comprises (a) one V_L1, and (b) one of V_L2, V_L3, V_L4, V_L5, V_L6, V_L7, V_L8, V_L9, V_L10, V_L11, V_L12, V_L13, V_L14, V_L15, V_L16, V_L17, or V_L18. Again another example of such an antigen binding protein comprises (a) one V_L2, and (b) one of V_L1, V_L3, V_L4, V_L5, V_L6, V_L7, V_L8, V_L9, V_L10, V_L11 or V_L12. Again another example of such an antigen binding protein comprises (a) one V_L3, and (b) one of V_L1, V_L2, V_L4, V_L5, V_L6, V_L7, V_L8, V_L9, V_L10, V_L11, V_L12, V_L13, V_L14, V_L15, V_L16, V_L17, or V_L18, etc.

The various combinations of heavy chain variable regions can be combined with any of the various combinations of light chain variable regions.

In other embodiments, an antigen binding protein comprises two identical light chain variable regions and/or two identical heavy chain variable regions. As an example, the antigen binding protein can be an antibody or immunologically functional fragment thereof that includes two light chain variable regions and two heavy chain variable regions in combinations of pairs of light chain variable regions and pairs of heavy chain variable regions as listed in Tables 2A and 2B.

Some antigen binding proteins that are provided comprise a heavy chain variable domain comprising a sequence of amino acids that differs from the sequence of a heavy chain variable domain selected from V_H1, V_H2, V_H3, V_H4, V_H5, V_H6, V_H7, V_H8, V_H9, V_H10, V_H11, V_H12, V_H13, V_H14, V_H15, V_H16, V_H17 and V_H18 at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid, with the deletions, insertions and/or substitutions resulting in no more than 15 amino acid changes relative to the foregoing variable domain sequences. The heavy chain variable region in some antigen binding proteins comprises a sequence of amino acids that has at least 70%, 75%, 80%, 85%, 90%, 95%, 97% or 99% sequence identity to the amino acid sequences of the heavy chain variable region of V_H1, V_H2, V_H3, V_H4, V_H5, V_H6, V_H7, V_H8, V_H9, V_H10, V_H11, V_H12, V_H13, V_H14, V_H15, V_H16, V_H17 and V_H18.

Certain antigen binding proteins comprise a light chain variable domain comprising a sequence of amino acids that differs from the sequence of a light chain variable domain selected from V_L1, V_L2, V_L3, V_L4, V_L5, V_L6, V_L7, V_L8, V_L9, V_L10, V_L11, V_L12, V_L13, V_L14, V_L15, V_L16, V_L17 and V_L18 at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid, with the deletions, insertions and/or substitutions resulting in no more than 15 amino acid changes relative to the foregoing variable domain sequences. The light chain variable region in some antigen binding proteins comprises a sequence of amino acids that has at least 70%, 75%, 80%, 85%, 90%, 95%, 97% or 99% sequence identity to the amino acid sequences of the light chain variable region of V_L1, V_L2, V_L3, V_L4, V_L5, V_L6, V_L7, V_L8, V_L9, V_L10, V_L11, V_L12, V_L13, V_L14, V_L15, V_L16, V_L17 or V_L18.

In additional instances, antigen binding proteins comprise the following pairings of light chain and heavy chain variable domains: V_L1 with V_H1, V_L2 with V_H2, V_L2 with V_H3, V_L3 with V_H4, V_L4 with V_H5, V_L5 with V_H6, V_L6 with V_H7, V_L7 with V_H8, V_L8 with V_H8, V_L9 with V_H9, V_L9 with V_H10, V_L10 with V_H11, V_L11 with V_H11, V_L12 with V_H12, V_L13 with V_H13, V_L14 with V_H14, V_L15 with V_H15, V_L16 with V_H16, V_L17 with V_H17 and V_L18 with V_H18. In some instances, the antigen binding proteins in the above pairings can comprise amino acid sequences that have 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity with the specified variable domains.

Still other antigen binding proteins, e.g., antibodies or immunologically functional fragments, include variant forms of a variant heavy chain and a variant light chain as just described.

Antigen Binding Protein CDRs

In various embodiments, the antigen binding proteins disclosed herein can comprise polypeptides into which one or more CDRs are grafted, inserted and/or joined. An antigen binding protein can have 1, 2, 3, 4, 5 or 6 CDRs. An antigen binding protein thus can have, for example, one heavy chain CDR1 ("CDRH1"), and/or one heavy chain CDR2 ("CDRH2"), and/or one heavy chain CDR3 ("CDRH3"), and/or one light chain CDR1 ("CDRL1"), and/or one light chain CDR2 ("CDRL2"), and/or one light chain CDR3 ("CDRL3"). Some antigen binding proteins include both a CDRH3 and a CDRL3. Specific heavy and light chain CDRs are identified in Tables 3A and 3B, respectively and in Table 6C, infra.

Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody can be identified using the system described by Kabat et al., in Sequences of Proteins of Immunological Interest, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. As desired, the CDRs can also be redefined according an alternative nomenclature scheme, such as that of Chothia (see Chothia & Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia et al., 1989, *Nature* 342:878-883 or Honegger & Pluckthun, 2001, *J. Mol. Biol.* 309:657-670). Certain antibodies that are disclosed herein comprise one or more amino acid sequences that are identical or have substantial sequence identity to the amino acid sequences of one or more of the CDRs presented in Table 3A (CDRHs) and Table 3B (CDRLs) and Table 6C, infra.

TABLE 3A

Exemplary CDRH Sequences

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
20D4	121	V_H12	CDRH1-1	DLSMH
17C3	122	V_H1	CDRH1-2	NARMGVS
22H5		V_H2		
16H7		V_H3		
24H11		V_H4		
18B11.1	123	V_H11	CDRH1-3	DAWMS
18B11.2		V_H11		
18G1	124	V_H5	CDRH1-4	TYAMS
12C11		V_H8		
12E4		V_H8		
17D8		V_H6		
26H11		V_H7		
21B4	125	V_H10	CDRH1-5	SYFWS
46D11	126	V_H13	CDRH1-6	NARMGVN
37D3	127	V_H15	CDRH1-7	NAWMS
39F11	128	V_H17	CDRH1-8	SYGIH
39G5		V_H18		
39F7	129	V_H16	CDRH1-9	NYGIH
40D2	130	V_H14	CDRH1-10	SGGYNWS
21H2	131	V_H9	CDRH1-11	SYYWS
20D4	132	V_H12	CDRH2-1	GFDPEDGETIYAQKFQG
17C3	133	V_H1	CDRH2-2	HIFSNDEKSYSTSLKS
22H5		V_H2		
16H7		V_H3		
46D11		V_H13		
24H11	134	V_H4	CDRH2-3	HIFSNDEKSYSTSLKN
18B11.1	135	V_H11	CDRH2-4	RIKSKTDGGTTDYAAP VKG
18B11.2		V_H11		
37D3		V_H15		
18G1	136	V_H5	CDRH2-5	GISGSGVSTHYADSVKG
12C11	137	V_H8	CDRH2-6	GISGSGVSTYYADSVKG
12E4		V_H8		
17D8	138	V_H6	CDRH2-7	AISGSGVSTYYADSVKG
26H11	139	V_H7	CDRH2-8	AISGSGVSTNYADSVKG
21B4	140	V_H10	CDRH2-9	RIYTSGSTNYNPSLKS
21H2		V_H9		
39F11	141	V_H17	CDRH2-10	VIWYDGSDKYYADSVKG
39F7	142	V_H16	CDRH2-11	VIWYDGSIKYYADSVKG
39G5	143	V_H18	CDRH2-12	VIWYDGSDKYYGDSVKG
40D2	144	V_H14	CDRH2-13	NIYYSGSTYYNPSLKS
20D4	145	V_H12	CDRH3-1	IVVVPAAIQSYYYYY GMGV
17C3	146	V_H1	CDRH3-2	ILLLGAYYYYGMDV
22H5	147	V_H2	CDRH3-3	ILLVGAYYYCGMDV
16H7	148	V_H3	CDRH3-4	SVVTGGYYYDGMDV
24H11		V_H4		

TABLE 3A-continued

Exemplary CDRH Sequences

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
18B11.1	149	V_H11	CDRH3-5	TYSSGWYVWDYYGMDV
18B11.2		V_H11		
18G1	150	V_H5	CDRH3-6	SLIVVIVYALDH
12C11	151	V_H8	CDRH3-7	SLIVVIVYALDY
12E4		V_H8		
17D8	152	V_H6	CDRH3-8	SLIVVMVYVLDY
26H11		V_H7		
21B4	153	V_H10	CDRH3-9	DPDGDYYYYGMDV
21H2		V_H9		
46D11	154	V_H13	CDRH3-10	VRIAGDYYYYYGMDV
37D3	155	V_H15	CDRH3-11	DRVLSYYAMAV
39F11	156	V_H17	CDRH3-12	DRAAAGLHYYYGMDV
39F7		V_H16		
39G5		V_H18		
40D2	157	V_H14	CDRH3-13	ENIVVIPAAIFAGWFDP

TABLE 3B

Exemplary CDRL Sequences

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
20D4	158	V_L12	CDRL1-1	RASQDIRYDLG
18B11.1	159	V_L10	CDRL1-2	RSSQSLLYYNGFTYLD
12C11	160	V_L8	CDRL1-3	RASQNFDSSSLA
18G1	161	V_L4	CDRL1-4	RASQNFDSSYLA
17D8	162	V_L5	CDRL1-5	RASQSVSGNYLA
26H11		V_L6		
21B4	163	V_L9	CDRL1-6	RASQSVSSTYLA
21H2		V_L9		
39F7		V_L16		
39F11		V_L17		
39G5		V_L18		
12E4	164	V_L7	CDRL1-7	RASQNFDSNYLA
18B11.2	165	V_L11	CDRL1-8	RASQSVNSNLA
16H7	166	V_L3	CDRL1-9	GGNNIGSESVH
24H11		V_L3		
22H5	167	V_L2	CDRL1-10	GGNNIGSQSVH
17C3		V_L1		
46D11	168	V_L13	CDRL1-11	RASQGISIWLA
40D2	169	V_L14	CDRL1-12	KSSQSLLQSDGKTYLY
37D3	170	V_L15	CDRL1-13	RSSQSLLHSNGYNFLD
20D4	171	V_L12	CDRL2-1	AASSLQS
46D11		V_L13		

TABLE 3B-continued

Exemplary CDRL Sequences

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
18B11.1	172	V_L10	CDRL2-2	LGSNRAS
12C11	173	V_L8	CDRL2-3	GASSRAT
17D8		V_L5		
21B4		V_L9		
21H2		V_L9		
26H11		V_L6		
12E4		V_L7		
39F7		V_L16		
39F11		V_L17		
18G1	174	V_L4	CDRL2-4	GTSSRAT
18B11.2	175	V_L11	CDRL2-5	GVSTRAT
16H7	176	V_L3	CDRL2-6	DDSDRPS
24H11		V_L3		
22H5		V_L2		
17C3		V_L1		
40D2	177	V_L14	CDRL2-7	EVSNRFS
37D3	178	V_L15	CDRL2-8	LGSDRAS
39G5	179	V_L18	CDRL2-9	GASFRAT
20D4	180	V_L12	CDRL3-1	LQHNSYPLT
18B11.1	181	V_L10	CDRL3-2	MQSLQTPFT
12C11	182	V_L8	CDRL3-3	QQCGSSPLT
18G1	183	V_L4	CDRL3-4	QQYGGSPLT
17D8	184	V_L5	CDRL3-5	QQYGSAPLT
21B4	185	V_L9	CDRL3-6	QQYGSSFT
21H2		V_L9		
26H11	186	V_L6	CDRL3-7	QQYGSSPLT
12E4		V_L7		
18B11.2	187	V_L11	CDRL3-8	QQYNNWPPT
16H7	188	V_L3	CDRL3-9	QVWDGNSDHVV
24H11		V_L3		
22H5	189	V_L2	CDRL3-10	QVWDNTSDHVV
17C3	190	V_L1	CDRL3-11	QVWDSSSDHVV
46D11	191	V_L13	CDRL3-12	QQANDFPIT
40D2	192	V_L14	CDRL3-13	MQSIQLPRT
37D3	193	V_L15	CDRL3-14	MQALQTPCS
39F7	194	V_L16	CDRL3-15	QQSGSSPLT
39F11		V_L17		
39G5		V_L18		

TABLE 3C

Coding Sequences for CDRHs

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
20D4	195	V_H12	CDRH 1-1	GATTTATCCATGCAC
17C3 22H5 16H7 24H11	196	V_H1 V_H2 V_H3 V_H4	CDRH 1-2	AATGCTAGAATGGGTGTGAGC
18B11.1 18B11.2	197	V_H11 V_H11	CDRH 1-3	GACGCCTGGATGAGC
18G1 12C11 12E4 17D8 26H11	198	V_H5 V_H8 V_H8 V_H6 V_H7	CDRH 1-4	ACCTATGCCATGAGC
21B4 21H2	199	V_H10 V_H9	CDRH 1-5	AGTTACTTCTGGAGC
46D11	200	V_H13	CDRH 1-6	AATGCTAGAATGGGTGTGAAC
37D3	201	V_H15	CDRH 1-7	AACGCCTGGATGAGC
39F11 39G5	202	V_H17 V_H18	CDRH 1-8	AGCTATGGCATCCAC
39F7	203	V_H16	CDRH 1-9	AACTATGGCATTCAC
40D2	204	V_H14	CDRH 1-10	AGTGGTGGTTACAACTGGAGC
20D4	205	V_H12	CDRH 2-1	GGTTTTGATCCTGAAGATGGTGAAACAATCT ACGCACAGAAGTTCCAGGGC
17C3 22H5 16H7 46D11	206	V_H1 V_H2 V_H3 V_H13	CDRH 2-2	CACATTTTTTCGAATGACGAAAAA TCCTACAGCACATCTCTGAAGAGC
24H11	207	V_H4	CDRH 2-3	CACATTTTTTCGAATGACGAAAAATC CTACAGCACATCTCTGAAGAAC
18B11.1 18B11.2 37D3	208	V_H11 V_H11 V_H15	CDRH 2-4	CGTATTAAAAGCAAAACTGATGGTGGGA CAACAGACTACGCTGCACCCGTGAAAGGC
18G1	209	V_H5	CDRH 2-5	GGTATTAGTGGTAGTGGTGTCAGCACACA CTACGCAGACTCCGTGAAGGGC
12C11 12E4	210	V_H8 V_H8	CDRH 2-6	GGTATTAGTGGTAGTGGTGTTAGCACATAC TACGCAGACTCCGTGAAGGGC
17D8	211	V_H6	CDRH 2-7	GCTATCAGTGGTAGTGGTGTTAGCACATAC TACGCAGACTCCGTGAAGGGC
26H11	212	V_H7	CDRH 2-8	GCTATTAGTGGCAGTGGTGTGAGCACAAAC TACGCAGACTCCGTGAAGGGC
21B4 21H2	213	V_H10 V_H9	CDRH 2-9	CGTATCTATACCAGTGGGAGCACCAACTACA ACCCCTCCCTCAAGAGT
39F11	214	V_H17	CDRH 2-10	GTTATATGGTATGATGGAAGTGATAAATACTA TGCAGACTCCGTGAAGGGC
39F7	215	V_H16	CDRH 2-11	GTTATATGGTATGATGGAAGTATTAAATACTA TGCAGACTCCGTGAAGGGC
39G5	216	V_H18	CDRH 2-12	GTTATATGGTATGATGGAAGTGATAAATACTA TGGAGACTCCGTGAAGGGC

TABLE 3C-continued

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
			Coding Sequences for CDRHs	
40D2	217	V_H14	CDRH 2-13	AACATCTATTACAGTGGGAGCACCTACTACAA CCCGTCCCTCAAGAGT
20D4	218	V_H12	CDRH 3-1	ATTGTAGTAGTCCCAGCTGCTATACAGAGTTA CTACTACTACTACGGTATGGGCGTC
17C3	219	V_H1	CDRH 3-2	ATATTATTACTGGGAGCTTACTACTACTACGG TATGGACGTC
22H5	220	V_H2	CDRH 3-3	ATATTATTAGTGGGAGCTTACTACTACTGCGG TATGGACGTC
16H7 24H11	221	V_H3 V_H4	CDRH 3-4	TCAGTAGTAACTGGCGGCTACTACTACGACG GTATGGACGTC
18B11.1 18B11.2	222	V_H11 V_H11	CDRH 3-5	ACGTATAGCAGTGGCTGGTACGTATGGGAC TACTACGGTATGGACGTC
18G1	223	V_H5	CDRH 3-6	TCCCTCATTGTAGTAATAGTATATGCCCTTG ACCAC
12C11 12E4	224	V_H8 V_H8	CDRH 3-7	TCCCTTATTGTAGTAATAGTATATGCCCT TGACTAC
17D8 26H11	225	V_H6 V_H7	CDRH 3-8	TCCCTTATTGTAGTAATGGTGTATGTCCT TGACTAC
21B4 21H2	226	V_H10 V_H9	CDRH 3-9	GATCCGGACGGTGACTACTACTACTACG GTATGGACGTC
46D11	227	V_H13	CDRH 3-10	GTTCGTATAGCAGGTGATTACTACTACTA CTACGGTATGGACGTC
37D3	228	V_H15	CDRH 3-11	GATCGGGTGCTAAGCTACTACGCTATGG CCGTC
39F11 39F7 39G5	229	V_H17 V_H16 V_H18	CDRH 3-12	GATAGGGCAGCAGCTGGTCTCCACTATT ATTACGGTATGGACGTC
40D2	230	V_H14	CDRH 3-13	GAGAATATTGTAGTAATACCAGCTGCTAT ATTCGCGGGTTGGTTCGACCCC

TABLE 3D

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
			Coding Sequences for CDRLs	
20D4	231	V_L12	CDRL1-1	CGGGCAAGTCAGGACATTAGATATGATT TAGGC
18B11.1	232	V_L10	CDRL1-2	AGGTCTAGTCAGAGCCTCCTGTATTATA ATGGATTCACCTATTTGGAT
12C11	233	V_L8	CDRL1-3	AGGGCCAGTCAGAATTTTGACAGCAGC TCCTTAGCC
18G1	234	V_L4	CDRL1-4	AGGGCCAGTCAGAATTTTGACAGCAGT TACTTAGCC
17D8 26H11	235	V_L5 V_L6	CDRL1-5	AGGGCCAGTCAGAGTGTTAGCGGCAAC TACTTGGCC
21B4 21H2 39F7 39F11 39G5	236	V_L9 V_L9 V_L16 V_L17 V_L18	CDRL1-6	AGGGCCAGTCAGAGTGTGAGCAGTACC TACTTAGCC

TABLE 3D-continued

Coding Sequences for CDRLs				
Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
12E4	237	V_L7	CDRL1-7	AGGGCCAGTCAGAATTTCGACAGCAAC TACTTAGCC
18B11.2	238	V_L11	CDRL1-8	AGGGCCAGTCAGAGTGTTAACAGCAAC TTAGCC
16H7 24H11	239	V_L3 V_L3	CDRL1-9	GGGGGAAACAACATTGGAAGTGAAAGTG TGCAC
22H5 17C3	240	V_L2 V_L1	CDRL1-10	GGGGGAAACAACATTGGAAGTCAAAGTG TGCAC
46D11	241	V_L13	CDRL1-11	CGGGCGAGTCAGGGTATTAGCATCTGGT TAGCC
40D2	242	V_L14	CDRL1-12	AAGTCTAGTCAGAGCCTCCTACAGAGTG ATGGAAAGACCTATTTGTAT
37D3	243	V_L15	CDRL1-13	AGGTCTAGTCAGAGCCTCCTGCATAGTA ATGGATACAACTTTTTGGAT
20D4 46D11	244	V_L12 V_L13	CDRL2-1	GCTGCATCCAGTTTGCAAAGT
18B11.1	245	V_L10	CDRL2-2	TTGGGTTCTAATCGGGCCTCC
12C11 17D8 21B4 21H2 26H11 12E4 39F7 39F11	246	V_L8 V_L5 V_L9 V_L9 V_L6 V_L7 V_L16 V_L17	CDRL2-3	GGTGCATCCAGCAGGGCCACT
18G1	247	V_L4	CDRL2-4	GGTACATCCAGCAGGGCCACT
18B11.2	248	V_L11	CDRL2-5	GGTGTATCCACCAGGGCCACT
16H7 24H11 22H5 17C3	249	V_L3 V_L3 V_L2 V_L1	CDRL2-6	GATGATAGCGACCGGCCCTCA
40D2	250	V_L14	CDRL2-7	GAAGTTTCCAACCGATTCTCT
37D3	251	V_L15	CDRL2-8	TTGGGTTCTGATCGGGCCTCC
20D4	252	V_L12	CDRL3-1	CTACAGCATAATAGTTACCCTCTCACT
18B11.1	253	V_L10	CDRL3-2	ATGCAGTCTCTGCAAACTCCATTCACT
12C11	254	V_L8	CDRL3-3	CAGCAGTGTGGTAGCTCACCGCTCACT
18G1	255	V_L4	CDRL3-4	CAGCAGTATGGTGGCTCACCGCTCACT
17D8	256	V_L5	CDRL3-5	CAGCAGTATGGTAGCGCACCGCTCACT
21B4 21H2	257	V_L9 V_L9	CDRL3-6	CAGCAGTATGGAAGTTCATTCACT
26H11 12E4	258	V_L6 V_L7	CDRL3-7	CAGCAGTATGGTAGCTCACCGCTCACT
18B11.2	259	V_L11	CDRL3-8	CAGCAGTATAATAACTGGCCTCCGACG
16H7 24H11	260	V_L3 V_L3	CDRL3-9	CAGGTGTGGGATGGTAATAGTGATCAT GTGGTA
22H5	261	V_L2	CDRL3-10	CAGGTGTGGGATAATACTAGTGATCAT GTGGTA

TABLE 3D-continued

Coding Sequences for CDRLs				
Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
17C3	262	V_L1	CDRL3-11	CAGGTGTGGGATAGTAGTAGTGATCAT GTGGTA
46D11	263	V_L13	CDRL3-12	CAACAGGCTAACGATTTCCCGATCACC
40D2	264	V_L14	CDRL3-13	ATGCAAAGTATACAGCTTCCTCGGACG
37D3	265	V_L15	CDRL3-14	ATGCAAGCTCTACAAACTCCGTGCAGT
39F7 39F11 39G5	266	V_L16 V_L17 V_L18	CDRL3-15	CAGCAGTCTGGTAGCTCACCTCTCACT

The structure and properties of CDRs within a naturally occurring antibody has been described, supra. Briefly, in a traditional antibody, the CDRs are embedded within a framework in the heavy and light chain variable region where they constitute the regions responsible for antigen binding and recognition. A variable region comprises at least three heavy or light chain CDRs, see, supra (Kabat et al., 1991, *Sequences of Proteins of Immunological Interest*, Public Health Service N.I.H., Bethesda, Md.; see also Chothia and Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia et al., 1989, *Nature* 342: 877-883), within a framework region (designated framework regions 1-4, FR1, FR2, FR3, and FR4, by Kabat et al., 1991; see also Chothia and Lesk, 1987, supra). The CDRs provided herein, however, can not only be used to define the antigen binding domain of a traditional antibody structure, but can be embedded in a variety of other polypeptide structures, as described herein.

In one aspect, the CDRs provided are (a) a CDRH selected from the group consisting of (i) a CDRH1 selected from the group consisting of SEQ ID NO:121-131; (ii) a CDRH2 selected from the group consisting of SEQ ID NO:132-144; (iii) a CDRH3 selected from the group consisting of SEQ ID NO:145-157; and (iv) a CDRH of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than five, four, three, two, or one amino acids; (B) a CDRL selected from the group consisting of (i) a CDRL1 selected from the group consisting of SEQ ID NO:158-170; (ii) a CDRL2 selected from the group consisting of SEQ ID NO:171-179; (iii) a CDRL3 selected from the group consisting of SEQ ID NO:180-194; and (iv) a CDRL of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than 1, 2, 3, 4, or 5 amino acids amino acids.

In another aspect, an antigen binding protein comprises 1, 2, 3, 4, 5, or 6 variant forms of the CDRs listed in Tables 3A and 3B and Table 6C, infra, each having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to a CDR sequence listed in Tables 3A and 3B and Table 6C, infra. Some antigen binding proteins comprise 1, 2, 3, 4, 5, or 6 of the CDRs listed in Tables 3A and 3B and Table 6C, infra, each differing by no more than 1, 2, 3, 4 or 5 amino acids from the CDRs listed in these tables.

In still another aspect, an antigen binding protein includes the following associations of CDRL1, CDRL2 and CDRL3: SEQ ID NOs:167, 176, and 190; SEQ ID NOs:167, 176, and 189, SEQ ID NOs:166, 176, and 188; SEQ ID NOs:166, 176, and 188; SEQ ID NOs:161, 174, and 183; SEQ ID NOs:162, 173, and 184; SEQ ID NOs:162, 173, and 186; SEQ ID NOs:164, 173, and 186; SEQ ID NOs:160, 173, and 182; SEQ ID NOs:163, 173, and 185; SEQ ID NOs:163, 173, and 185; SEQ ID NOs:159, 172, and 181; SEQ ID NOs:165, 175, and 187; SEQ ID NOs:158, 171, and 180; SEQ ID NOs:168, 171, and 191; SEQ ID NOs:169, 177 and 192; SEQ ID NOs:170, 178, and 193; SEQ ID NOs:163, 173, and 194; SEQ ID NOs:163, 173 and 194; and SEQ ID NOs:163, 179, and 194.

In an additional aspect, an antigen binding protein includes the following associations of CDRH1, CDRH2 and CDRH3: SEQ ID NOs:122, 133, and 146; SEQ ID NOs:122, 133, and 147; SEQ ID NOs:122, 133, and 148; SEQ ID NOs:122, 134, and 148; SEQ ID NOs:124, 136, and 150; SEQ ID NOs:124, 138, and 152; SEQ ID NOs:124, 139, and 152; SEQ ID NOs:124, 137, and 151; SEQ ID NOs:124, 137, and 151; SEQ ID NOs:131, 140, and 153; SEQ ID NOs:125, 140, and 153; SEQ ID NOs:123, 135, and 149; SEQ ID NOs:123, 135, and 149; SEQ ID NOs:121, 132, and 145; SEQ ID NOs:126, 133, and 154; SEQ ID NOs:130, 144, and 157; SEQ ID NOs:127, 135, and 155; SEQ ID NOs:129, 142, and 156; SEQ ID NOs:128, 141, and 156; and SEQ ID NOs:128, 143, and 156.

In another aspect, an antigen binding protein includes the following associations of CDRL1, CDRL2 and CDRL3 with CDRH1, CDRH2 and CDRH3: SEQ ID NOs:167, 176, and 190; SEQ ID NOs:167, 176, and 189, SEQ ID NOs:166, 176, and 188; SEQ ID NOs:166, 176, and 188; SEQ ID NOs:161, 174, and 183; SEQ ID NOs:162, 173, and 184; SEQ ID NOs:162, 173, and 186; SEQ ID NOs:164, 173, and 186; SEQ ID NOs:160, 173, and 182; SEQ ID NOs:163, 173, and 185; SEQ ID NOs:163, 173, and 185; SEQ ID NOs:159, 172, and 181; SEQ ID NOs:165, 175, and 187; SEQ ID NOs:158, 171, and 180; SEQ ID NOs:168, 171, and 191; SEQ ID NOs:169, 177 and 192; SEQ ID NOs:170, 178, and 193; SEQ ID NOs: 163, 173, and 194; SEQ ID NOs:163, 173 and 194; SEQ ID NOs:163, 179, and 194 with SEQ ID NOs:122, 133, and 146; SEQ ID NOs:122, 133, and 147; SEQ ID NOs:122, 133, and 148; SEQ ID NOs:122, 134, and 148; SEQ ID NOs:124, 136, and 150; SEQ ID NOs:124, 138, and 152; SEQ ID NOs:124, 139, and 152; SEQ ID NOs:124, 137, and 151; SEQ ID NOs:124, 137, and 151; SEQ ID NOs:131, 140, and 153; SEQ ID NOs:125, 140, and 153; SEQ ID NOs:123, 135, and 149; SEQ ID NOs:123, 135, and 149; SEQ ID NOs:121, 132, and 145; SEQ ID NOs:126, 133, and 154; SEQ ID NOs:130, 144, and 157; SEQ ID NOs:127, 135, and 155; SEQ ID NOs:129, 142, and 156; SEQ ID NOs:128, 141, and 156; and SEQ ID NOs:128, 143, and 156.

Consensus Sequences

In yet another aspect, the CDRs disclosed herein include consensus sequences derived from groups of related monoclonal antibodies. As described herein, a "consensus sequence" refers to amino acid sequences having conserved amino acids common among a number of sequences and variable amino acids that vary within a given amino acid sequences. The CDR consensus sequences provided include CDRs corresponding to each of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3.

Consensus sequences were determined using standard analyses of the CDRs corresponding to the V_H and V_L of the disclosed antibodies, some of which specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. The consensus sequences were determined by keeping the CDRs contiguous within the same sequence corresponding to a V_H or V_L.

Light Chain CDR3

Group 1
LQHNSYPLT (SEQ ID NO: 267)

Group 2
MQSLQTPFT (SEQ ID NO: 268)

Group 3
QQYNNWPPT (SEQ ID NO: 269)

Group 4
MQSIQLPRT (SEQ ID NO: 270)

Group 5
QQANDFPIT (SEQ ID NO: 271)

Group 6
MQALQTPCS (SEQ ID NO: 272)

Group 7
QVWD G N SDHVV (SEQ ID NO: 273)

QVWD N T SDHVV (SEQ ID NO: 274)

QVWD S S SDHVV (SEQ ID NO: 275)

QVWD X_1 X_2 SDHVV (SEQ ID NO: 276)

wherein X_1 is G, S or N and X_2 is S, T or N.

Group 8
QQ C G S S P L T (SEQ ID NO: 277)

QQ Y G G S P L T (SEQ ID NO: 278)

QQ Y G S A P L T (SEQ ID NO: 279)

QQ Y G S S F T (SEQ ID NO: 280)

QQ Y G S S P L T (SEQ ID NO: 281)

QQ S G S S P L T (SEQ ID NO: 282)

QQ X_3 G X_4 X_5 X_6 X_7 T (SEQ ID NO: 283)

wherein X_3 is C, Y or S, X_4 is S or G, X_5 is S or A, X_6 is P or F and X_7 is L or absent.

Light Chain CDR2

Group 1
AASSLQS (SEQ ID NO: 284)

Group 2
GVSTRAT (SEQ ID NO: 285)

-continued

Group 3
DDSDRPS (SEQ ID NO: 286)

Group 4
EVSNRFS (SEQ ID NO: 287)

Group 5
L G S N R A S (SEQ ID NO: 288)

L G S D R A S (SEQ ID NO: 289)

L G S X_{27} R A S (SEQ ID NO: 290)

wherein X_{27} is N or D.

Group 6
G A S S RAT (SEQ ID NO: 291)

G T S S RAT (SEQ ID NO: 292)

G A S F RAT (SEQ ID NO: 293)

G X_8 S X_{28} RAT (SEQ ID NO: 294)

wherein X_8 is A or T and X_{28} is S or F.

Light Chain CDR1

Group 1
RASQSVNSNLA (SEQ ID NO: 295)

Group 2
RASQDIRYDLG (SEQ ID NO: 296)

Group 3
RASQGISIWLA (SEQ ID NO: 297)

Group 4
KSSQSLLQSDGKTYLY (SEQ ID NO: 298)

Group 5
RASQ N F D S S S LA (SEQ ID NO: 299)

RASQ N F D S S Y LA (SEQ ID NO: 300)

RASQ S V S G N Y LA (SEQ ID NO: 301)

RASQ S V S G T Y LA (SEQ ID NO: 302)

RASQ N F D S N Y LA (SEQ ID NO: 303)

RASQ X_9 X_{10} X_{11} X_{12} X_{13} X_{14} LA (SEQ ID NO: 304)

wherein X_9 is A or S, X_{10} is V or F, X_{11} is D or S, X_{12} is G or S, X_{13} is S, N or T, and X_{14} is S or Y.

Group 6
GGNNIGS E SVH (SEQ ID NO: 305)

GGNNIGS Q SVH (SEQ ID NO: 306)

GGNNIGS X_{15} SVH (SEQ ID NO: 307)

wherein X_{15} is E or Q.

Group 7
RSSQSLL Y Y NG F T Y LD (SEQ ID NO: 308)

RSSQSLL H S NG Y N F LD (SEQ ID NO: 309)

RSSQSLL X_{29} X_{30} NG X_{31} X_{32} X_{33} LD (SEQ ID NO: 310)

wherein X_{29} is Y or H, X_{30} is Y or S, X_{31} is F or Y, X_{32} is T or N and X_{33} is Y or F.

Heavy CDR3

Group 1
IVVVPAAIQSYYYYYGMGV (SEQ ID NO: 311)

Group 2
DPDGDYYYYGMDV (SEQ ID NO: 312)

Group 3
TYSSGWYVWDYYGMDV (SEQ ID NO: 313)

Group 4
DRVLSYYAMAV (SEQ ID NO: 314)

Group 5
VRIAGDYYYYYGMDV (SEQ ID NO: 315)

Group 6
ENIVVIPAAIFAGWFDP (SEQ ID NO: 316)

Group 7
DRAAAGLHYYYGMDV (SEQ ID NO: 317)

Group 8
I L L L G A YYY Y GMDV (SEQ ID NO: 318)

I L L V G A YYY C GMDV (SEQ ID NO: 319)

V V T G G YYY D GMDV (SEQ ID NO: 320)

S V V T G G YYY D GMDV (SEQ ID NO: 321)

X_{34} X_{16} X_{17} X_{18} G X_{19} YYY X_{20} GMDV (SEQ ID NO: 322)

Wherein X_{34} is I, V or S, X_{16} is L or V, X_{17} is L, T or V, X_{18} is L, V, G or T, X_{19} is A, G or absent and X_{20} is Y, C or D.

Group 9
SLIVV I VY A LD H (SEQ ID NO: 323)

SLIVV I VY A LD Y (SEQ ID NO: 324)

SLIVV M VY V LD Y (SEQ ID NO: 325)

SLIVV X_{21} VY X_{22} LD X_{23} (SEQ ID NO: 326)

Wherein X_{21} is I or M, X_{22} is A or V and X_{23} is H or Y.

Heavy CDR2

Group 1
GFDPEDGETIYAQKFQG (SEQ ID NO: 327)

Group 2
RIKSK T DGGTTDYAAPVKG (SEQ ID NO: 328)

RIKSK DGGTTDYAAPVKG (SEQ ID NO: 330)

RIKSK X_{42} DGGTTDYAAPVKG (SEQ ID NO: 483)

wherein X_{42} is T or absent.

Group 3
HIFSNDEKSYSTSLK S (SEQ ID NO: 331)

HIFSNDEKSYSTSLK N (SEQ ID NO: 332)

HIFSNDEKSYSTSLK X_{24} (SEQ ID NO: 333)

wherein X_{24} is S or N.

Group 4
G ISGSGVST H YADSVKG (SEQ ID NO: 334)

G ISGSGVST Y YADSVKG (SEQ ID NO: 335)

A ISGSGVST Y YADSVKG (SEQ ID NO: 336)

-continued

A ISGSGVST N YADSVKG (SEQ ID NO: 337)

X_{25} ISGSGVST X_{26} YADSVKG (SEQ ID NO: 338)

wherein X_{25} is G or A and X_{26} is H, Y or N.

Group 5
VIWYDGS D KYY A DSVKG (SEQ ID NO: 339)

VIWYDGS I KYY G DSVKG (SEQ ID NO: 340)

VIWYDGS X_{35} KYY X_{36} DSVKG (SEQ ID NO: 341)

wherein X_{35} is D or I and X_{36} is A or G.

Group 6
N IY Y SGST Y YNPSLKS (SEQ ID NO: 342)

R IY T SGST Y YNPSLKS (SEQ ID NO: 343)

R IY T SGST N YNPSLKS (SEQ ID NO: 329)

X_{37} IY X_{38} SGST X_{41} YNPSLKS (SEQ ID NO: 344)

wherein X_{37} is N or R, X_{38} is Y or T and X_{41} is Y or N.

Heavy CDR1

Group 1
DLSMH (SEQ ID NO: 345)

Group 2
DAWMS (SEQ ID NO: 346)

Group 3
TYAMS (SEQ ID NO: 347)

Group 4
SYFWS (SEQ ID NO: 348)

Group 5
SGGYNWS (SEQ ID NO: 349)

Group 6
NARMGV S (SEQ ID NO: 350)

NARMGV N (SEQ ID NO: 351)

NARMGV X_{39} (SEQ ID NO: 352)

wherein X_{39} is S or N.

Group 7
S YGIH (SEQ ID NO: 353)

N YGIH (SEQ ID NO: 354)

X_{40} YGIH (SEQ ID NO: 355)

wherein X_{40} is S or N.

In some cases an antigen binding protein comprises at least one heavy chain CDR1, CDR2, or CDR3 having one of the above consensus sequences. In some cases, an antigen binding protein comprises at least one light chain CDR1, CDR2, or CDR3 having one of the above consensus sequences. In other cases, the antigen binding protein comprises at least two heavy chain CDRs according to the above consensus sequences, and/or at least two light chain CDRs according to the above consensus sequences. In still other cases, the antigen binding protein comprises at least three heavy chain CDRs according to the above consensus sequences, and/or at least three light chain CDRs according to the above consensus sequences.

Exemplary Antigen Binding Proteins

According to one aspect, an isolated antigen binding protein comprising (a) one or more heavy chain complementary determining regions (CDRHs) selected from the group consisting of: (i) a CDRH1 selected from the group consisting of SEQ ID NO:121-131; (ii) a CDRH2 selected from the group consisting of SEQ ID NO:132-144; (iii) a CDRH3 selected from the group consisting of SEQ ID NO:145-157; and (iv) a CDRH of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than 1, 2, 3, 4, or 5 amino acids; (b) one or more light chain complementary determining regions (CDRLs) selected from the group consisting of: (i) a CDRL1 selected from the group consisting of SEQ ID NO:158-170; (ii) a CDRL2 selected from the group consisting of SEQ ID NO:171-179; (iii) a CDRL3 selected from the group consisting of SEQ ID NO:180-194; and (iv) a CDRL of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than five, four, three, four, two or one amino acids; or (c) one or more heavy chain CDRHs of (a) and one or more light chain CDRLs of (b).

In another embodiment, the CDRHs have at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO:121-157, and/or the CDRLs have at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO:158-194. In a further embodiment, the VH is selected from the group consisting of SEQ ID NO:121-157, and/or the VL is selected from the group consisting of SEQ ID NO: 158-194.

According to one aspect, an isolated antigen binding protein comprising (a) one or more variable heavy chains (VHs) selected from the group consisting of: (i) SEQ ID NO:121-157; and (ii) a VH of (i) that contains one or more amino acid substitutions, deletions or insertions of no more than five, four, three, four, two or one amino acids; (b) one or more variable light chains (VLs) selected from the group consisting of: (i) SEQ ID NO:158-194, and (ii) a VL of (i) that contains one or more amino acid substitutions, deletions or insertions of no more than five, four, three, four, two or one amino acids; or (c) one or more variable heavy chains of (a) and one or more variable light chains of (b).

In another embodiment, the variable heavy chain (VH) has at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO:121-157, and/or the variable light chain (VL) has at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 158-194.

In one aspect, also provided is an antigen binding protein that specifically binds to an epitope comprising one or more amino acid residues from FGFR1c, FGRF2c, FGFR3c, and FGFR4.

In one aspect, also provided is an antigen binding protein that specifically binds to an epitope comprising one or more amino acid residues from β-Klotho.

In another aspect, also provided is an isolated antigen binding protein that specifically binds to an epitope comprising one or more amino acid residues from both β-Klotho and one or more amino acid residues from FGFR1c, FGFR2c, FGFR3c, or FGFR4.

In yet another embodiment, the isolated antigen binding protein described hereinabove comprises a first amino acid sequence comprising at least one of the CDRH consensus sequences disclosed herein, and a second amino acid sequence comprising at least one of the CDRL consensus sequences disclosed herein.

In one aspect, the first amino acid sequence comprises at least two of the CDRH consensus sequences, and/or the second amino acid sequence comprises at least two of the CDRL consensus sequences. In certain embodiments, the first and the second amino acid sequence are covalently bonded to each other.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:146, the CDRH2 of SEQ ID NO:133, and the CDRH1 of SEQ ID NO:122, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:190, the CDRL2 of SEQ ID NO:176, and the CDRL1 of SEQ ID NO:167.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:147, the CDRH2 of SEQ ID NO:133, and the CDRH1 of SEQ ID NO:122, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:189, the CDRL2 of SEQ ID NO:176, and the CDRL1 of SEQ ID NO:167.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:148, the CDRH2 of SEQ ID NO:133, and the CDRH1 of SEQ ID NO:122, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:188, the CDRL2 of SEQ ID NO:176, and the CDRL1 of SEQ ID NO:166.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:148, the CDRH2 of SEQ ID NO:134, and the CDRH1 of SEQ ID NO:122, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:188, the CDRL2 of SEQ ID NO:176, and the CDRL1 of SEQ ID NO:166.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:150, the CDRH2 of SEQ ID NO:136, and the CDRH1 of SEQ ID NO:124, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:183, the CDRL2 of SEQ ID NO:174, and the CDRL1 of SEQ ID NO:161.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:152, the CDRH2 of SEQ ID NO:138, and the CDRH1 of SEQ ID NO:124, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:184, the CDRL2 of SEQ ID NO:173, and the CDRL1 of SEQ ID NO:162.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:152, the CDRH2 of SEQ ID NO:139, and the CDRH1 of SEQ ID NO:124, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:186, the CDRL2 of SEQ ID NO:173, and the CDRL1 of SEQ ID NO:162.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:151, the CDRH2 of SEQ ID NO:137, and the CDRH1 of SEQ ID NO:124, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:186, the CDRL2 of SEQ ID NO:173, and the CDRL1 of SEQ ID NO:164.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:151, the CDRH2 of SEQ ID NO:137, and the CDRH1 of SEQ ID NO:124, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:182, the CDRL2 of SEQ ID NO:173, and the CDRL1 of SEQ ID NO:160.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:153, the CDRH2 of SEQ ID NO:140, and the CDRH1 of SEQ ID NO:131, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:185, the CDRL2 of SEQ ID NO:173, and the CDRL1 of SEQ ID NO:163.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:153, the CDRH2 of SEQ ID NO:140, and the CDRH1 of SEQ ID NO:125, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:185, the CDRL2 of SEQ ID NO:173, and the CDRL1 of SEQ ID NO:163.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:149, the CDRH2 of SEQ ID NO:135, and the CDRH1 of SEQ ID NO:123, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:181, the CDRL2 of SEQ ID NO:172, and the CDRL1 of SEQ ID NO:159.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:149, the CDRH2 of SEQ ID NO:135, and the CDRH1 of SEQ ID NO:123, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:187, the CDRL2 of SEQ ID NO:175, and the CDRL1 of SEQ ID NO:165.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:145, the CDRH2 of SEQ ID NO:132, and the CDRH1 of SEQ ID NO:121, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:180, the CDRL2 of SEQ ID NO:171, and the CDRL1 of SEQ ID NO:158.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:154, the CDRH2 of SEQ ID NO:133, and the CDRH1 of SEQ ID NO:126, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:191, the CDRL2 of SEQ ID NO:171, and the CDRL1 of SEQ ID NO:168.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:157, the CDRH2 of SEQ ID NO:144, and the CDRH1 of SEQ ID NO:130, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:192, the CDRL2 of SEQ ID NO:177, and the CDRL1 of SEQ ID NO:169.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:155, the CDRH2 of SEQ ID NO:135, and the CDRH1 of SEQ ID NO:127, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:193, the CDRL2 of SEQ ID NO:178, and the CDRL1 of SEQ ID NO:170.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:156, the CDRH2 of SEQ ID NO:142, and the CDRH1 of SEQ ID NO:129, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:194, the CDRL2 of SEQ ID NO:173, and the CDRL1 of SEQ ID NO:163.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:156, the CDRH2 of SEQ ID NO:141, and the CDRH1 of SEQ ID NO:128, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:194, the CDRL2 of SEQ ID NO:173, and the CDRL1 of SEQ ID NO:163.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein comprises the CDRH3 of SEQ ID NO:156, the CDRH2 of SEQ ID NO:143, and the CDRH1 of SEQ ID NO:128, and/or the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NO:194, the CDRL2 of SEQ ID NO:179, and the CDRL1 of SEQ ID NO:163.

In a further embodiment, the antigen binding protein comprises at least two CDRH sequences of heavy chain sequences H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17 or H18, as shown in Table 4A. In again a further embodiment, the antigen binding protein comprises at least two CDRL sequences of light chain sequences L1, L2, L3, L4, L5, L6, L7, L8, L9, L10, L11, L12, L13, L14, L15, L16, L17 or L18, as shown in Table 4B. In still a further embodiment, the antigen binding protein comprises at least two CDRH sequences of heavy chain sequences H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17 or H18 as shown in Table 4A, and at least two CDRLs of light chain sequences L1, L2, L3, L4, L5, L6, L7, L8, L9, L10, L11, L12, L13, L14, L15, L16, L17 or L18 as shown in Table 4B.

In again another embodiment, the antigen binding protein comprises the CDRH1, CDRH2, and CDRH3 sequences of heavy chain sequences H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17 or H18 as shown in Table 4A. In yet another embodiment, the antigen binding protein comprises the CDRL1, CDRL2, and CDRL3 sequences of light chain sequences L1, L2, L3, L4, L5, L6, L7, L8, L9, L10, L11, L12, L13, L14, L15, L16, L17 or L18 as shown in Table 4B.

In yet another embodiment, the antigen binding protein comprises all six CDRs of L1 and H1, or L2 and H2, or L3 and H3, or L3 and H4, or L4 and H5, or L5 and H6, or L6 and H7, or L7 and H8, or L8 and H7, or L9 and H9, or L9 and H10, or L10 and H11, or L11 and H11, or L12 and H12, or L13 and H13, or L14 and H14, or L15 and H15, or L16 and H16, or L17 and H17, or L18 and H18, as shown in Tables 4A and 4B.

TABLE 4A

Heavy Chain Sequences							
Ref	Full Heavy (H#)	Full Heavy SEQ ID NO	Variable Heavy (VH#)	Variable Heavy SEQ ID NO	CDRH1 SEQ ID NO	CDRH2 SEQ ID NO	CDRH3 SEQ ID NO
17C3	H1	30	V_H1	66	122	133	146
22H5	H2	31	V_H2	67	122	133	147
16H7	H3	32	V_H3	68	122	133	148
24H11	H4	33	V_H4	69	122	134	148
18G1	H5	34	V_H5	70	124	136	150

TABLE 4A-continued

Heavy Chain Sequences

Ref	Full Heavy (H#)	Full Heavy SEQ ID NO	Variable Heavy (VH#)	Variable Heavy SEQ ID NO	CDRH1 SEQ ID NO	CDRH2 SEQ ID NO	CDRH3 SEQ ID NO
17D8	H6	35	V_H6	71	124	138	152
26H11	H7	36	V_H7	72	124	139	152
12E4	H8	37	V_H8	73	124	137	151
12C11	H7	37	V_H8	73	124	137	151
21H2	H9	38	V_H9	74	131	140	153
21B4	H10	39	V_H10	75	125	140	153
18B11.1	H11	40	V_H11	76	123	135	149
18B11.2	H11	40	V_H11	77	123	135	149
20D4	H12	41	V_H12	78	121	132	145
46D11	H13	42	V_H13	79	126	133	154
40D2	H14	46	V_H14	80	130	144	157
39F7	H16	44	V_H16	82	129	142	156
39F11	H17	43	V_H17	83	128	141	156
37D3	H15	47	V_H15	81	127	135	155
39G5	H18	45	V_H18	84	128	143	156

TABLE 4B

Light Chain Sequences

Ref	Full Light (L#)	Full Light SEQ ID NO	Variable Light (VH#)	Variable Light SEQ ID NO	CDRL1 SEQ ID NO	CDRL2 SEQ ID NO	CDRL3 SEQ ID NO
17C3	L1	48	V_L1	85	167	176	190
22H5	L2	49	V_L2	86	167	176	189
16H7	L3	50	V_L3	87	166	176	188
24H11	L3	50	V_L3	87	166	176	188
18G1	L4	51	V_L4	88	161	174	183
17D8	L5	52	V_L5	89	162	173	184
26H11	L6	53	V_L6	90	162	173	186
12E4	L7	54	V_L7	91	164	173	186
12C11	L8	55	V_L8	92	160	173	182
21H2	L9	56	V_L9	93	163	173	185
21B4	L9	56	V_L9	93	163	173	185
18B11.1	L10	57	V_L10	94	159	172	181
18B11.2	L11	58	V_L11	95	165	175	187
20D4	L12	59	V_L12	96	158	171	180
46D11	L13	60	V_L13	97	168	171	191
40D2	L14	61	V_L14	98	169	177	192
39F7	L16	63	V_L16	100	163	173	194
37D3	L15	62	V_L15	99	170	178	193
39F11	L17	64	V_L17	101	163	173	194
39G5	L18	65	V_L18	102	163	179	194

In one aspect, the isolated antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 provided herein can be a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof.

In another embodiment, the antibody fragment of the isolated antigen-binding proteins provided herein can be a Fab fragment, a Fab' fragment, an $F(ab')_2$ fragment, an Fv fragment, a diabody, or a single chain antibody molecule.

In a further embodiment, an isolated antigen binding protein that specifically (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 provided herein is a human antibody and can be of the IgG1-, IgG2-, IgG3- or IgG4-type.

In another embodiment, an isolated antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 comprises a light or a heavy chain polypeptide as set forth in Tables 1A-1B. In some embodiments, an antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 comprises a variable light or variable heavy domain such as those listed in Tables 2A-2B. In still other embodiments, an antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 comprises one, two or three CDRHs or one, two or three CDRLs as set forth in Tables 3A-3B, 4A-4B and Table 6C, infra. Such antigen binding proteins, and indeed any of the antigen binding proteins disclosed herein, can be PEGylated with one or more PEG molecules, for examples PEG molecules having a molecular weight selected from the group consisting of 5K, 10K, 20K, 40K, 50K, 60K, 80K, 100K or greater than 100K.

In yet another aspect, any antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 provided herein can be coupled to a labeling group and can compete for binding to the extracellular portion of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with an antigen binding protein of one of the isolated antigen binding proteins provided herein. In one embodiment, the isolated antigen binding protein provided herein can reduce blood glucose levels, decrease triglyceride and cholesterol levels or improve other glycemic parameters and cardiovascular risk factors when administered to a patient.

As will be appreciated, for any antigen binding protein comprising more than one CDR provided in Tables 3A-3B, and 4A-4B, any combination of CDRs independently selected from the depicted sequences may be useful. Thus, antigen binding proteins with one, two, three, four, five or six of independently selected CDRs can be generated. However, as will be appreciated by those in the art, specific embodiments generally utilize combinations of CDRs that are non-repetitive, e.g., antigen binding proteins are generally not made with two CDRH2 regions, etc.

Some of the antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are provided herein are discussed in more detail below.

Antigen Binding Proteins and Binding Epitopes and Binding Domains

When an antigen binding protein is said to bind an epitope on (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, or the extracellular domain of β-Klotho, FGFR1c, FGFR2c, FGFR3c or FGFR4, for example, what is meant is that the antigen binding protein specifically binds to a specified portion of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In some embodiments, e.g., in certain cases where the antigen binding protein binds only FGFR1c or β-Klotho, the antigen binding protein can specifically bind to a polypeptide consisting of specified residues (e.g., a specified segment of β-Klotho, FGFR1c, FGFR2c, FGFR3c or FGFR4, such as those residues disclosed in Example 14). In other embodiments, e.g., in certain cases where an antigen binding protein interacts with both β-Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4, the antigen binding protein can bind residues, sequences of residues, or regions in both β-Klotho and FGFR1c, FGFR2c, FGFR3c or FGFR4, depending on which receptor the antigen binding protein recognizes. In still other embodiments the antigen binding protein will bind residues, sequence or residues or regions of a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, for example FGFR1c.

In any of the foregoing embodiments, such an antigen binding protein does not need to contact every residue of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, or the extracellular domain of the recited proteins or complexes. Nor does every single amino acid substitution or deletion within (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, or the extracellular domain of the recited proteins or complexes, necessarily significantly affect binding affinity.

Epitope specificity and the binding domain(s) of an antigen binding protein can be determined by a variety of methods. Some methods, for example, can use truncated portions of an antigen. Other methods utilize antigen mutated at one or more specific residues, such as by employing an alanine scanning or arginine scanning-type approach or by the generation and study of chimeric proteins in which various domains, regions or amino acids are swapped between two proteins (e.g., mouse and human forms of one or more of the antigens or target proteins), or by protease protection assays.

Competing Antigen Binding Proteins

In another aspect, antigen binding proteins are provided that compete with one of the exemplified antibodies or functional fragments for binding to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Such antigen binding proteins can also bind to the same epitope as one of the herein exemplified antigen binding proteins, or an overlapping epitope. Antigen binding proteins and fragments that compete with or bind to the same epitope as the exemplified antigen binding proteins are expected to show similar functional properties. The exemplified antigen binding proteins and fragments include those with the heavy and light chains H1-H18 and L1-L18, variable region domains V_L1-V_L18 and V_H1-V_H18, and CDRs provided herein, including those in Tables 1, 2, 3, and 4. Thus, as a specific example, the antigen binding proteins that are provided include those that compete with an antibody comprising:

(a) 1, 2, 3, 4, 5 or all 6 of the CDRs listed for an antibody listed in Tables 3A and 3B, and 4A and 4B and Table 6C, infra;

(b) a V_H and a V_L selected from V_L1-V_L18 and V_H1-V_H18 and listed for an antibody listed in Tables 2A and 2B; or

(c) two light chains and two heavy chains as specified for an antibody listed in Tables 1A and 12B and Table 6A, infra.

Thus, in one embodiment, the present disclosure provides antigen binding proteins that competes for binding to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with a reference antibody, wherein the reference antibody comprises a combination of light chain and heavy chain variable domain sequences selected from the group consisting of L1H1, L2H2, L3H3, L3H4, L4H5, L5H6, L6H7, L7H8, L8H8, L9H9, L9H10, L10H11, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17 or L18H18. In another embodiment, the present disclosure provides human antibodies that compete for binding to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with a reference antibody, wherein the reference antibody is 17C3, 22H5, 16H7, 24H11, 18G1, 17D8, 26H11, 12E4, 12C11, 21H2, 21B4, 18B11.1, 18B11.2, 20D4, 46D11, 40D2, 37D3, 39F7, 39F1 or 39G5.

In a further embodiment, an isolated human antibody is provided that binds to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with substantially the same Kd as a reference antibody; initiates FGF21-like signaling in an in vitro ELK-Luciferase assay to the same degree as a reference antibody; lowers blood glucose; lowers serum lipid levels; and/or competes for binding with said reference antibody to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, wherein the reference antibody is selected from the group consisting of 17C3, 22H5, 16H7, 24H11, 18G1, 17D8, 26H11, 12E4, 12C11, 21H2, 21B4, 18B11.1, 18B11.2, 20D4, 46D11, 40D2, 37D3, 39F7, 39F1 or 39G5.

The ability to compete with an antibody can be determined using any suitable assay, such as that described in Example 8, in which antigen binding proteins 17C3, 22H5, 16H7, 24H11, 18G1, 17D8, 26H11, 12E4, 12C11, 21H2, 21B4, 18B11.1, 18B11.2, 20D4, 46D11, 40D2, 37D3, 39F7, 39F1 or 39G5 can be used as the reference antibody.

Monoclonal Antibodies

The antigen binding proteins that are provided include monoclonal antibodies that bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, and induce FGF21-like signaling to various degrees. Monoclonal antibodies can be produced using any technique known in the art, e.g., by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, e.g., by fusing them with myeloma cells to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in mouse fusions include Sp-20, P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XXO Bul; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

In some instances, a hybridoma cell line is produced by immunizing an animal (e.g., a transgenic animal having human immunoglobulin sequences) with a FGFR1c, β-Klotho or FGFR1c and/or β-Klotho immunogen (e.g., a soluble complex comprising the extracellular domains of FGFR1c, FGFR2c, FGFR3c or FGFR4 and/or β-Klotho as shown in Examples 2, and 3; membranes on which the extracellular domains of FGFR1c, FGFR2c, FGFR3c or FGFR4 and/or β-Klotho are expressed, as shown in Examples 1 and 3; or whole cells expressing FGFR1c and/or β-Klotho, as shown in Examples 1 and 3); harvesting spleen cells from the immunized animal; fusing the harvested spleen cells to a myeloma cell line, thereby generating hybridoma cells; establishing hybridoma cell lines from the hybridoma cells, and identifying a hybridoma cell line that produces an antibody that binds to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 (e.g., as described in the Example 4) and can induce FGF21-like signaling (e.g., as described in Examples 5-7). Such hybridoma cell lines, and the monoclonal antibodies produced by them, form aspects of the present disclosure.

Monoclonal antibodies secreted by a hybridoma cell line can be purified using any technique known in the art. Hybridomas or mAbs can be further screened to identify mAbs with particular properties, such as the ability to induce FGF21-like signaling. Examples of such screens are provided herein.

Chimeric and Humanized Antibodies

Chimeric and humanized antibodies based upon the foregoing sequences can readily be generated. One example is a chimeric antibody, which is an antibody composed of protein segments from different antibodies that are covalently joined to produce functional immunoglobulin light or heavy chains or immunologically functional portions thereof. Generally, a portion of the heavy chain and/or light chain is identical with or homologous to a corresponding sequence in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. For methods relating to chimeric antibodies, see, for example, U.S. Pat. No. 4,816,567; and Morrison et al., 1985, *Proc. Natl. Acad. Sci. USA* 81:6851-6855, which are hereby incorporated by reference. CDR grafting is described, for example, in U.S. Pat. Nos. 6,180,370, 5,693,762, 5,693,761, 5,585,089, and 5,530,101.

Generally, the goal of making a chimeric antibody is to create a chimera in which the number of amino acids from the intended patient/recipient species is maximized. One example is the "CDR-grafted" antibody, in which the antibody comprises one or more complementarity determining regions (CDRs) from a particular species or belonging to a particular antibody class or subclass, while the remainder of the antibody chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. For use in humans, the variable region or selected CDRs from a rodent antibody often are grafted into a human antibody, replacing the naturally-occurring variable regions or CDRs of the human antibody.

One useful type of chimeric antibody is a "humanized" antibody. Generally, a humanized antibody is produced from a monoclonal antibody raised initially in a non-human animal. Certain amino acid residues in this monoclonal antibody, typically from non-antigen recognizing portions of the antibody, are modified to be homologous to corresponding residues in a human antibody of corresponding isotype. Humanization can be performed, for example, using various methods by substituting at least a portion of a rodent variable region for the corresponding regions of a human antibody (see, e.g., U.S. Pat. Nos. 5,585,089, and 5,693,762; Jones et al., 1986, *Nature* 321:522-525; Riechmann et al., 1988, *Nature* 332:323-27; Verhoeyen et al., 1988, *Science* 239:1534-1536).

In one aspect, the CDRs of the light and heavy chain variable regions of the antibodies provided herein (e.g., in Tables 3 and 4) are grafted to framework regions (FRs) from antibodies from the same, or a different, phylogenetic species. For example, the CDRs of the heavy and light chain variable regions V_H1, V_H2, V_H3, V_H4, V_H5, V_H6, V_H7, V_H8, V_H9, V_H10, V_H11, V_H12, V_H13, V_H14, V_H15, V_H16, V_H17 or V_H18 and/or V_L1, V_L2, V_L3, V_L4, V_L5, V_L6, V_L7, V_L8, V_L9, V_L10, V_L,11, V_H12, V_L13, V_L14, V_L15, V_L16, V_L17 or V_L18 can be grafted to consensus human FRs. To create consensus human FRs, FRs from several human heavy chain or light chain amino acid sequences can be aligned to identify a consensus amino acid sequence. In other embodiments, the FRs of a heavy chain or light chain disclosed herein are replaced with the FRs from a different heavy chain or light chain. In one aspect, rare amino acids in the FRs of the heavy and light chains of an antigen binding protein (e.g., an antibody) that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 are not replaced, while the rest of the FR amino acids are replaced. A "rare amino acid" is a specific amino acid that is in a position in which this particular amino acid is not usually found in an FR. Alternatively, the grafted variable regions from the one heavy or light chain can be used with a constant region that is different from the constant region of that particular heavy or light chain as disclosed herein. In other embodiments, the grafted variable regions are part of a single chain Fv antibody.

In certain embodiments, constant regions from species other than human can be used along with the human variable region(s) to produce hybrid antibodies.

Fully Human Antibodies

Fully human antibodies are also provided by the instant disclosure. Methods are available for making fully human antibodies specific for a given antigen without exposing human beings to the antigen ("fully human antibodies"). One specific means provided for implementing the production of fully human antibodies is the "humanization" of the mouse humoral immune system. Introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated is one means of producing fully human monoclonal antibodies (mAbs) in mouse, an animal that can be immunized with any desirable antigen. Using fully human antibodies can minimize the immunogenic and allergic responses that can sometimes be caused by administering mouse or mouse-derived mAbs to humans as therapeutic agents.

Fully human antibodies can be produced by immunizing transgenic animals (typically mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production. Antigens for this purpose typically have six or more contiguous amino acids, and optionally are conjugated to a carrier, such as a hapten. See, e.g., Jakobovits et al., (1993) *Proc. Natl. Acad. Sci. USA* 90:2551-2555; Jakobovits et al., (1993) *Nature* 362:255-258; and Bruggermann et al., (1993) *Year in Immunol.* 7:33. In one example of such a method, transgenic animals are produced by incapacitating the endogenous mouse immunoglobulin loci encoding the mouse heavy and light immunoglobulin chains therein, and inserting into the mouse genome large fragments of human genome DNA containing loci that encode human heavy and light chain proteins. Partially modified animals, which have less than the full complement of human immunoglobulin loci, are then cross-bred to obtain an animal having all of the desired immune system modifications. When administered an immunogen, these transgenic animals produce antibodies that are immunospecific for the immunogen but have human rather than murine amino acid sequences, including the variable regions. For further details of such methods, see, e.g., WO96/33735 and WO94/02602. Additional methods relating to transgenic mice for making human antibodies are described in U.S. Pat. Nos. 5,545,807; 6,713,610; 6,673,986; 6,162,963; 5,545,807; 6,300,129; 6,255,458; 5,877,397; 5,874,299 and 5,545,806; in PCT publications WO91/10741, WO90/04036, and in EP 546073B1 and EP 546073A1.

The transgenic mice described above, referred to herein as "HuMab" mice, contain a human immunoglobulin gene minilocus that encodes unrearranged human heavy ([μ, mu] and [γ, gamma]) and [κ, kappa] light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ [mu] and κ [kappa] chain loci (Lonberg et al., 1994, *Nature* 368:856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or [κ, kappa] and in response to immunization, and the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgG [κ, kappa] monoclonal antibodies (Lonberg et al., supra.; Lonberg and Huszar, (1995) *Intern. Rev. Immunol.* 13: 65-93; Harding and Lonberg, (1995) *Ann. N.Y. Acad. Sci.* 764:536-546). The preparation of HuMab mice is described in detail in Taylor et al., (1992) *Nucleic Acids Research* 20:6287-6295; Chen et al., (1993) *International Immunology* 5:647-656; Tuaillon et al., (1994) *J. Immunol.* 152:2912-2920; Lonberg et al., (1994) *Nature* 368:856-859; Lonberg, (1994) *Handbook of Exp. Pharmacology* 113:49-101; Taylor et al., (1994) *International Immunology* 6:579-591; Lonberg and Huszar, (1995) *Intern. Rev. Immunol.* 13:65-93; Harding and Lonberg, (1995) *Ann. N.Y. Acad. Sci.* 764:536-546; Fishwild et al., (1996) *Nature Biotechnology* 14:845-851; the foregoing references are hereby incorporated by reference in their entirety for all purposes. See, further U.S. Pat. Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; and 5,770,429; as well as U.S. Pat. No. 5,545,807; International Publication Nos. WO 93/1227; WO 92/22646; and WO 92/03918, the disclosures of all of which are hereby incorporated by reference in their entirety for all purposes. Technologies utilized for producing human antibodies in these transgenic mice are disclosed also in WO 98/24893, and Mendez et al., (1997) *Nature Genetics* 15:146-156, which are hereby incorporated by reference. For example, the HCo7 and HCo12 transgenic mice strains can be used to generate antigen binding proteins (e.g., antibodies) that bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and may induce FGF21-like signaling. Further details regarding the production of human antibodies using transgenic mice are provided in the examples below.

Using hybridoma technology, antigen-specific human mAbs with the desired specificity can be produced and selected from the transgenic mice such as those described above. Such antibodies can be cloned and expressed using a suitable vector and host cell, or the antibodies can be harvested from cultured hybridoma cells.

Fully human antibodies can also be derived from phage-display libraries (as disclosed in Hoogenboom et al., (1991) *J. Mol. Biol.* 227:381; and Marks et al., (1991) *J. Mol. Biol.* 222:581). Phage display techniques mimic immune selection through the display of antibody repertoires on the surface of filamentous bacteriophage, and subsequent selection of phage by their binding to an antigen of choice. One such technique is described in PCT Publication No. WO 99/10494 (hereby incorporated by reference), which describes the isolation of high affinity and functional agonistic antibodies for MPL- and msk-receptors using such an approach.

Bispecific or Bifunctional Antigen Binding Proteins

Also provided are bispecific and bifunctional antibodies that include one or more CDRs or one or more variable regions as described above. A bispecific or bifunctional antibody in some instances can be an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai and Lachmann, 1990, *Clin. Exp. Immunol.* 79:315-321; Kostelny et al., 1992, *J. Immunol.* 148:1547-1553. When an antigen binding protein of the instant disclosure binds (i) both β-Klotho and one or more of FGFR1c, FGFR2c, FGFR3c or FGFR4; or (ii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, the binding may lead to the activation of FGF21-like activity as measured by the FGF21-like functional and signaling assays described in Examples 5-7; when such an antigen binding protein is an antibody it is referred to as an agonistic antibody.

Various Other Forms

Some of the antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are provided in the present disclosure include variant forms of the antigen binding proteins disclosed herein (e.g., those having the sequences listed in Tables 1-4).

In various embodiments, the antigen binding proteins disclosed herein can comprise one or more non-naturally occurring amino acids. For instance, some of the antigen binding proteins have one or more non-naturally occurring amino acid substitutions in one or more of the heavy or light chains, variable regions or CDRs listed in Tables 1-4. Examples of non-naturally amino acids (which can be substituted for any naturally-occurring amino acid found in any sequence disclosed herein, as desired) include: 4-hydroxyproline, γ-carboxyglutamate, ϵ-N,N,N-trimethyllysine, ϵ-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ-N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxyl-terminal direction, in accordance with standard usage and convention. A non-limiting lists of examples of non-naturally occurring amino acids that can be inserted into an antigen binding protein sequence or substituted for a wild-type residue in an antigen binding sequence include β-amino acids, homoamino acids, cyclic amino acids and amino acids with derivatized side chains. Examples include (in the L-form or D-form; abbreviated as in parentheses): citrulline (Cit), homocitrulline (hCit), Nα-methylcitrulline (NMeCit), Nα-methylhomocitrulline (Nα-MeHoCit), ornithine (Orn), Nα-Methylornithine (Nα-MeOrn or NMeOrn), sarcosine (Sar), homolysine (hLys or hK), homoarginine (hArg or hR), homoglutamine (hQ), Nα-methylarginine (NMeR), Nα-methylleucine (Nα-MeL or NMeL), N-methylhomolysine (NMeHoK), Nα-methylglutamine (NMeQ), norleucine (Nle), norvaline (Nva), 1,2,3,4-tetrahydroisoquinoline (Tic), Octahydroindole-2-carboxylic acid (Oic), 3-(1-naphthyl)alanine (1-Nal), 3-(2-naphthyl) alanine (2-Nal), 1,2,3,4-tetrahydroisoquinoline (Tic), 2-indanylglycine (IgI), para-iodophenylalanine (pI-Phe), para-aminophenylalanine (4AmP or 4-Amino-Phe), 4-guanidino phenylalanine (Guf), glycyllysine (abbreviated "K(Nϵ-glycyl)" or "K(glycyl)" or "K(gly)"), nitrophenylalanine (nitrophe), aminophenylalanine (aminophe or Amino-Phe), benzylphenylalanine (benzylphe), γ-carboxyglutamic acid (γ-carboxyglu), hydroxyproline (hydroxypro), p-carboxyl-phenylalanine (Cpa), α-aminoadipic acid (Aad), Nα-methyl valine (NMeVal), N-α-methyl leucine (NMeLeu), Nα-methylnorleucine (NMeNle), cyclopentylglycine (Cpg), cyclohexylglycine (Chg), acetylarginine (acetylarg), α, β-diaminopropionoic acid (Dpr), α, γ-diaminobutyric acid (Dab), diaminopropionic acid (Dap), cyclohexylalanine (Cha), 4-methyl-phenylalanine (MePhe), β, β-diphenyl-alanine (BiPhA), aminobutyric acid (Abu), 4-phenyl-phenylalanine (or biphenylalanine; 4Bip), α-amino-isobutyric acid (Aib), beta-alanine, beta-aminopropionic acid, piperidinic acid, aminocaprioic acid, aminoheptanoic acid, aminopimelic acid, desmosine, diaminopimelic acid, N-ethylglycine, N-ethylaspargine, hydroxylysine, allo-hydroxylysine, isodesmosine, allo-isoleucine, N-methylglycine, N-methylisoleucine, N-methylvaline, 4-hydroxyproline (Hyp), γ-carboxyglutamate, ϵ-N,N,N-trimethyllysine, ϵ-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, ω-methylarginine, 4-Amino-O-Phthalic Acid (4APA), and other similar amino acids, and derivatized forms of any of those specifically listed.

Additionally, the antigen binding proteins can have one or more conservative amino acid substitutions in one or more of the heavy or light chains, variable regions or CDRs listed in Tables 1-4. Naturally-occurring amino acids can be divided into classes based on common side chain properties:

1) hydrophobic: norleucine, Met, Ala, Val, Leu, Ile;
2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;
3) acidic: Asp, Glu;
4) basic: His, Lys, Arg;
5) residues that influence chain orientation: Gly, Pro; and
6) aromatic: Trp, Tyr, Phe.

Conservative amino acid substitutions can involve exchange of a member of one of these classes with another member of the same class. Conservative amino acid substitutions can encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. See Table 5, infra. These include peptidomimetics and other reversed or inverted forms of amino acid moieties.

Non-conservative substitutions can involve the exchange of a member of one of the above classes for a member from another class. Such substituted residues can be introduced into regions of the antibody that are homologous with human antibodies, or into the non-homologous regions of the molecule.

In making such changes, according to certain embodiments, the hydropathic index of amino acids can be considered. The hydropathic profile of a protein is calculated by assigning each amino acid a numerical value ("hydropathy index") and then repetitively averaging these values along the peptide chain. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

The importance of the hydropathic profile in conferring interactive biological function on a protein is understood in the art (see, e.g., Kyte et al., 1982, *J. Mol. Biol.* 157:105-131). It is known that certain amino acids can be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in certain embodiments, the substitution of amino acids whose hydropathic indices are within ±2 is included. In some aspects, those which are within ±1 are included, and in other aspects, those within ±0.5 are included.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigen-binding or immunogenicity, that is, with a biological property of the protein.

The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0±1); glutamate (+3.0±1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5±1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5) and tryptophan (−3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ±2 is included, in other embodiments, those which are within ±1 are included, and in still other embodiments, those within ±0.5 are included. In some instances, one can also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

Exemplary conservative amino acid substitutions are set forth in Table 5.

TABLE 5

Conservative Amino Acid Substitutions

Original Residue	Exemplary Substitutions
Ala	Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn, Gln
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile
Phe	Met, Leu, Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp, Phe
Val	Ile, Leu

A skilled artisan will be able to determine suitable variants of polypeptides as set forth herein using well-known techniques coupled with the information provided herein. One skilled in the art can identify suitable areas of the molecule that can be changed without destroying activity by targeting regions not believed to be important for activity. The skilled artisan also will be able to identify residues and portions of the molecules that are conserved among similar polypeptides. In further embodiments, even areas that can be important for biological activity or for structure can be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues important for activity or structure in similar proteins. One skilled in the art can opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

One skilled in the art can also analyze the 3-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of such information, one skilled in the art can predict the alignment of amino acid residues of an antibody with respect to its three dimensional structure. One skilled in the art can choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues can be involved in important interactions with other molecules. Moreover, one skilled in the art can generate test variants containing a single amino acid substitution at each desired amino acid residue. These variants can then be screened using assays for FGF21-like signaling, (see the Examples provided herein) thus yielding information regarding which amino acids can be changed and which must not be changed. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acid positions where further substitutions should be avoided either alone or in combination with other mutations.

A number of scientific publications have been devoted to the prediction of secondary structure. See, Moult, (1996) *Curr. Op. in Biotech.* 7:422-427; Chou et al., (1974) *Biochem.* 13:222-245; Chou et al., (1974) *Biochemistry* 113:211-222; Chou et al., (1978) *Adv. Enzymol. Relat. Areas Mol. Biol.* 47:45-148; Chou et al., (1979) *Ann. Rev. Biochem.* 47:251-276; and Chou et al., (1979) *Biophys. J.* 26:367-384. Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins that have a sequence identity of greater than 30%, or similarity greater than 40% can have similar structural topologies. The growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See, Holm et al., (1999) *Nucl. Acid. Res.* 27:244-247. It has been suggested (Brenner et al., (1997) *Curr. Op. Struct. Biol.* 7:369-376) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate.

Additional methods of predicting secondary structure include "threading" (Jones, (1997) *Curr. Opin. Struct. Biol.* 7:377-387; Sippl et al., (1996) *Structure* 4:15-19), "profile analysis" (Bowie et al., (1991) *Science* 253:164-170; Gribskov et al., (1990) *Meth. Enzym.* 183:146-159; Gribskov et al., (1987) *Proc. Nat. Acad. Sci.* 84:4355-4358), and "evolutionary linkage" (See, Holm, (1999) supra; and Brenner, (1997) supra).

In some embodiments, amino acid substitutions are made that: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter ligand or antigen binding affinities, and/or (4) confer or modify other physicochemical or functional properties on such polypeptides. For example, single or multiple amino acid substitutions (in certain embodiments, conservative amino acid substitutions) can be made in the naturally-occurring sequence. Substitutions can be made in that portion of the antibody that lies outside the domain(s) forming intermolecular contacts). In such embodiments, conservative amino acid substitutions can be used that do not substantially change the structural characteristics of the parent sequence (e.g., one or more replacement amino acids that do not disrupt the secondary structure that characterizes the parent or native antigen binding protein). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed.), 1984, W. H. New York: Freeman and Company; Introduction to *Protein Structure* (Branden and Tooze, eds.), 1991, New York: Garland Publishing; and Thornton et al., (1991) *Nature* 354:105, which are each incorporated herein by reference.

Additional preferred antibody variants include cysteine variants wherein one or more cysteine residues in the parent or native amino acid sequence are deleted from or substituted with another amino acid (e.g., serine). Cysteine variants are useful, inter alia when antibodies must be refolded into a biologically active conformation. Cysteine variants can have fewer cysteine residues than the native antibody, and typically have an even number to minimize interactions resulting from unpaired cysteines.

The heavy and light chains, variable regions domains and CDRs that are disclosed can be used to prepare polypeptides that contain an antigen binding region that can specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and may induce FGF21-like signaling. For example, one or more of the CDRs listed in Tables 3 and 4 can be incorporated into a molecule (e.g., a polypeptide) covalently or noncovalently to make an immunoadhesion. An immunoadhesion can incorporate the CDR(s) as part of a larger polypeptide chain, can covalently link the CDR(s) to another polypeptide chain, or can incorporate the CDR(s) noncovalently. The CDR(s) enable the immunoadhesion to bind specifically to a particular antigen of interest (e.g., (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 or an epitope thereon).

The heavy and light chains, variable regions domains and CDRs that are disclosed can be used to prepare polypeptides that contain an antigen binding region that can specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and may induce FGF21-like signaling. For example, one or more of the CDRs listed in Tables 3 and 4 can be incorporated into a molecule (e.g., a polypeptide) that is structurally similar to a "half" antibody comprising the heavy chain, the light chain of an antigen binding protein paired with a Fc fragment so that the antigen binding region is monovalent (like a Fab fragment) but with a dimeric Fc moiety.

Mimetics (e.g., "peptide mimetics" or "peptidomimetics") based upon the variable region domains and CDRs that are described herein are also provided. These analogs can be peptides, non-peptides or combinations of peptide and non-peptide regions. Fauchere, 1986, *Adv. Drug Res.* 15:29; Veber and Freidinger, 1985, *TINS* p. 392; and Evans et al., 1987, *J. Med. Chem.* 30:1229, which are incorporated herein by reference for any purpose. Peptide mimetics that are structurally similar to therapeutically useful peptides can be used to produce a similar therapeutic or prophylactic effect. Such compounds are often developed with the aid of computerized molecular modeling. Generally, peptidomimetics are proteins that are structurally similar to an antibody displaying a desired biological activity, such as here the ability to specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, but have one or more peptide linkages optionally replaced by a linkage selected from: —CH_2NH—, —CH_2S—, —CH_2—CH_2—, —CH—CH-(cis and trans), —$COCH_2$—, —CH(OH) CH_2—, and —CH_2SO—, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) can be used in certain embodiments to generate more stable proteins. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation can be generated by methods known in the art (Rizo and Gierasch, 1992, *Ann. Rev. Biochem.* 61:387), incorporated herein by reference), for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

Derivatives of the antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are described herein are also provided. The derivatized antigen binding proteins can comprise any molecule or substance that imparts a desired property to the antibody or fragment, such as increased half-life in a particular use. The derivatized antigen binding protein can comprise, for example, a detectable (or labeling) moiety (e.g., a radioactive, colorimetric, antigenic or enzymatic molecule, a detectable bead (such as a magnetic or electrodense (e.g., gold) bead), or a molecule that binds to another molecule (e.g., biotin or streptavidin)), a therapeutic or diagnostic moiety (e.g., a radioactive, cytotoxic, or pharmaceutically active moiety), or a molecule that increases the suitability of the antigen binding protein for a particular use (e.g., administration to a subject, such as a human subject, or other in vivo or in vitro uses). Examples of molecules that can be used to derivatize an antigen binding protein include albumin (e.g., human serum albumin) and polyethylene glycol (PEG). Albumin-linked and PEGylated derivatives of antigen binding proteins can be prepared using techniques well known in the art. Certain antigen binding proteins include a PEGylated single chain polypeptide as described herein. In one embodiment, the antigen binding protein is conjugated or otherwise linked to transthyretin (TTR) or a TTR variant. The TTR or TTR variant can be chemically modified with, for example, a chemical selected from the group consisting of dextran, poly(n-vinyl pyrrolidone), polyethylene glycols, propropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohols.

Other derivatives include covalent or aggregative conjugates of the antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are disclosed herein with other proteins or polypeptides, such as by expression of recombinant fusion proteins comprising heterologous polypeptides fused to the N-terminus or C-terminus of an antigen binding protein that induces FGF21-like signaling. For example, the conjugated peptide can be a heterologous signal (or leader) polypeptide, e.g., the yeast alpha-factor leader, or a peptide such as an epitope tag. An antigen binding protein-containing fusion protein of the present disclosure can comprise peptides added to facilitate purification or identification of an antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 (e.g., a poly-His tag) and that can induce FGF21-like signaling. An antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 also can be linked to the FLAG peptide as described in Hopp et al., 1988, *Bio/Technology* 6:1204; and U.S. Pat. No. 5,011,912. The FLAG peptide is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody (mAb), enabling rapid assay and facile purification of expressed recombinant protein. Reagents useful for preparing fusion proteins in which the FLAG peptide is fused to a given polypeptide are commercially available (Sigma, St. Louis, Mo.).

Multimers that comprise one or more antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and

FGFR4 form another aspect of the present disclosure. Multimers can take the form of covalently-linked or non-covalently-linked dimers, trimers, or higher multimers. Multimers comprising two or more antigen binding proteins that bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and which may induce FGF21-like signaling are contemplated for use as therapeutics, diagnostics and for other uses as well, with one example of such a multimer being a homodimer. Other exemplary multimers include heterodimers, homotrimers, heterotrimers, homotetramers, heterotetramers, etc.

One embodiment is directed to multimers comprising multiple antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 joined via covalent or non-covalent interactions between peptide moieties fused to an antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Such peptides can be peptide linkers (spacers), or peptides that have the property of promoting multimerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote multimerization of antigen binding proteins attached thereto, as described in more detail herein.

In particular embodiments, the multimers comprise from two to four antigen binding proteins that bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. The antigen binding protein moieties of the multimer can be in any of the forms described above, e.g., variants or fragments. Preferably, the multimers comprise antigen binding proteins that have the ability to specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In one embodiment, an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of fusion proteins comprising certain heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, e.g., by Ashkenazi et al., (1991) *Proc. Natl. Acad. Sci. USA* 88:10535; Byrn et al., (1990) *Nature* 344:677; and Hollenbaugh et al., 1992 "Construction of Immunoglobulin Fusion Proteins", in *Current Protocols in Immunology*, Suppl. 4, pages 10.19.1-10.19.11.

One embodiment comprises a dimer comprising two fusion proteins created by fusing an antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield the dimer.

The term "Fc polypeptide" as used herein includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

One suitable Fc polypeptide, described in PCT application WO 93/10151 and U.S. Pat. Nos. 5,426,048 and 5,262,522, is a single chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG1 antibody. Another useful Fc polypeptide is the Fc mutein described in U.S. Pat. No. 5,457,035, and in Baum et al., (1994) *EMBO J.* 13:3992-4001. The amino acid sequence of this mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. The mutein exhibits reduced affinity for Fc receptors.

In other embodiments, the variable portion of the heavy and/or light chains of a antigen binding protein such as disclosed herein can be substituted for the variable portion of an antibody heavy and/or light chain.

Alternatively, the oligomer is a fusion protein comprising multiple antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, with or without peptide linkers (spacer peptides). Among the suitable peptide linkers are those described in U.S. Pat. Nos. 4,751,180 and 4,935,233.

Another method for preparing oligomeric derivatives comprising that antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., (1988) *Science* 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe et al., (1994) *FEBS Letters* 344:191, hereby incorporated by reference. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow et al., (1994) *Semin. Immunol.* 6:267-278. In one approach, recombinant fusion proteins comprising an antigen binding protein fragment or derivative that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 is fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric antigen binding protein fragments or derivatives that form are recovered from the culture supernatant.

In certain embodiments, the antigen binding protein has a K_D (equilibrium binding affinity) of less than 1 pM, 10 pM, 100 pM, 1 nM, 2 nM, 5 nM, 10 nM, 25 nM or 50 nM.

In another aspect the instant disclosure provides an antigen binding protein having a half-life of at least one day in vitro or in vivo (e.g., when administered to a human subject). In one embodiment, the antigen binding protein has a half-life of at least three days. In another embodiment, the antibody or portion thereof has a half-life of four days or longer. In another embodiment, the antibody or portion thereof has a half-life of eight days or longer. In another embodiment, the antibody or portion thereof has a half-life of ten days or longer. In another embodiment, the antibody or portion thereof has a half-life of eleven days or longer. In another embodiment, the antibody or portion thereof has a half-life of fifteen days or longer. In another embodiment, the antibody or antigen-binding portion thereof is derivatized or modified such that it has a longer half-life as compared to the underivatized or unmodified antibody. In another embodiment, an antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 contains point mutations to increase serum half life, such as described in WO 00/09560, published Feb. 24, 2000, incorporated by reference.

Glycosylation

An antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can have a glycosylation pattern that is different or altered from that found in the native species. As is known in the art, glycosylation patterns can depend on both the sequence of the protein (e.g., the presence or absence of particular glycosylation amino acid residues, discussed below), or the host cell or organism in which the protein is produced. Particular expression systems are discussed below.

Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tri-peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tri-peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose, to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine can also be used.

Addition of glycosylation sites to the antigen binding protein is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tri-peptide sequences (for N-linked glycosylation sites). The alteration can also be made by the addition of, or substitution by, one or more serine or threonine residues to the starting sequence (for O-linked glycosylation sites). For ease, the antigen binding protein amino acid sequence can be altered through changes at the DNA level, particularly by mutating the DNA encoding the target polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the antigen binding protein is by chemical or enzymatic coupling of glycosides to the protein. These procedures are advantageous in that they do not require production of the protein in a host cell that has glycosylation capabilities for N- and O-linked glycosylation. Depending on the coupling mode used, the sugar(s) can be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO 87/05330 and in Aplin and Wriston, (1981) *CRC Crit. Rev. Biochem*., pp. 259-306.

Removal of carbohydrate moieties present on the starting antigen binding protein can be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the protein to the compound trifluoromethanesulfonic acid, or an equivalent compound. This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), while leaving the polypeptide intact. Chemical deglycosylation is described by Hakimuddin et al., (1987) *Arch. Biochem. Biophys.* 259:52 and by Edge et al., (1981) *Anal. Biochem.* 118:131. Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., (1987) *Meth. Enzymol.* 138:350. Glycosylation at potential glycosylation sites can be prevented by the use of the compound tunicamycin as described by Duskin et al., (1982) *J. Biol. Chem.* 257:3105. Tunicamycin blocks the formation of protein-N-glycoside linkages.

Hence, aspects of the present disclosure include glycosylation variants of antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 wherein the number and/or type of glycosylation site(s) has been altered compared to the amino acid sequences of the parent polypeptide. In certain embodiments, antibody protein variants comprise a greater or a lesser number of N-linked glycosylation sites than the native antibody. An N-linked glycosylation site is characterized by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X can be any amino acid residue except proline. The substitution of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions that eliminate or alter this sequence will prevent addition of an N-linked carbohydrate chain present in the native polypeptide. For example, the glycosylation can be reduced by the deletion of an Asn or by substituting the Asn with a different amino acid. In other embodiments, one or more new N-linked sites are created. Antibodies typically have a N-linked glycosylation site in the Fc region.

Labels and Effector Groups

In some embodiments, an antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 comprises one or more labels. The term "labeling group" or "label" means any detectable label. Examples of suitable labeling groups include, but are not limited to the following: radioisotopes or radionuclides (e.g., ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent groups (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic groups (e.g., horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, the labeling group is coupled to the antigen binding protein via spacer arms of various lengths to reduce potential steric hindrance. Various methods for labeling proteins are known in the art and can be used as is seen fit.

The term "effector group" means any group coupled to an antigen binding protein that specifically binds one (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that acts as a cytotoxic agent. Examples for suitable effector groups are radioisotopes or radionuclides (e.g., ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I). Other suitable groups include toxins, therapeutic groups, or chemotherapeutic groups. Examples of suitable groups include calicheamicin, auristatins, geldanamycin and cantansine. In some embodiments, the effector group is coupled to the antigen binding protein via spacer arms of various lengths to reduce potential steric hindrance.

In general, labels fall into a variety of classes, depending on the assay in which they are to be detected: a) isotopic labels, which can be radioactive or heavy isotopes; b) magnetic labels (e.g., magnetic particles); c) redox active moieties; d) optical dyes; enzymatic groups (e.g. horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase); e) biotinylated groups; and f) predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags, etc.). In some embodiments, the labeling group is coupled to the antigen binding protein via spacer arms of various lengths to reduce potential steric hindrance. Various methods for labeling proteins are known in the art.

Specific labels include optical dyes, including, but not limited to, chromophores, phosphors and fluorophores, with the latter being specific in many instances. Fluorophores can be either "small molecule" fluores, or proteinaceous fluores.

By "fluorescent label" is meant any molecule that can be detected via its inherent fluorescent properties. Suitable fluorescent labels include, but are not limited to, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malacite green, stilbene, Lucifer Yellow, Cascade Blue, Texas Red, IAEDANS, EDANS, BODIPY FL, LC Red 640, Cy 5, Cy 5.5, LC Red 705, Oregon green, the Alexa-Fluor dyes (Alexa Fluor 350, Alexa Fluor 430, Alexa Fluor 488, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 647, Alexa Fluor 660, Alexa Fluor 680), Cascade Blue, Cascade Yellow and R-phycoerythrin (PE) (Molecular Probes, Eugene, Oreg.), FITC, Rhodamine, and Texas Red (Pierce, Rockford, Ill.), Cy5, Cy5.5, Cy7 (Amersham Life Science, Pittsburgh, Pa.). Suitable optical dyes, including fluorophores, are described in MOLECULAR PROBES HANDBOOK by Richard P. Haugland, hereby expressly incorporated by reference.

Suitable proteinaceous fluorescent labels also include, but are not limited to, green fluorescent protein, including a *Renilla, Ptilosarcus*, or *Aequorea* species of GFP (Chalfie et al. (1994) *Science* 263:802-805), EGFP (Clontech Labs™, Inc., Genbank™ Accession Number U55762), blue fluorescent protein (BFP, Quantum Biotechnologies, Inc.™, Quebec, Canada; Stauber, (1998) *Biotechniques* 24:462-471; Heim et al., (1996) *Curr. Biol.* 6:178-182), enhanced yellow fluorescent protein (EYFP™, Clontech Labs™, Inc.), luciferase™ (Ichiki et al., (1993) *J.Immunol.* 150:5408-5417), β galactosidase (Nolan et al., (1988) *Proc. Natl. Acad. Sci. U.S.A.* 85:2603-2607) and *Renilla* (WO92/15673, WO95/07463, WO98/14605, WO98/26277, WO99/49019, U.S. Pat. Nos. 5,292,658, 5,418,155, 5,683,888, 5,741,668, 5,777,079, 5,804,387, 5,874,304, 5,876,995, 5,925,558).

Preparing Of Antigen Binding Proteins

Non-human antibodies that are provided can be, for example, derived from any antibody-producing animal, such as mouse, rat, rabbit, goat, donkey, or non-human primate (such as monkey (e.g., *cynomolgus* or rhesus monkey) or ape (e.g., chimpanzee)). Non-human antibodies can be used, for instance, in vitro cell culture and cell-culture based applications, or any other application where an immune response to the antibody does not occur or is insignificant, can be prevented, is not a concern, or is desired. In certain embodiments, the antibodies can be produced by immunizing with full-length β-Klotho, FGFR1c, FGFR2c, FGFR3c or FGFR4 (Example 1), with the extracellular domain of β-Klotho, FGFR1c, FGFR2c, FGFR3c or FGFR4 (Example 2), or two of β-Klotho, FGFR1c, FGFR2c, FGFR3c and FGFR4 (Example 1), with whole cells expressing FGFR1c, β-Klotho or both FGFR1c and β-Klotho (Example 1 and 3), with membranes prepared from cells expressing FGFR1c, β-Klotho or both FGFR1c and β-Klotho (Example 1 and 3), with fusion proteins, e.g., Fc fusions comprising FGFR1c, β-Klotho or FGFR1c and β-Klotho (or extracellular domains thereof) fused to Fc (Example 2 and 3), and other methods known in the art, e.g., as described in the Examples presented herein. Alternatively, the certain non-human antibodies can be raised by immunizing with amino acids which are segments of one or more of β-Klotho, FGFR1c, FGFR2c, FGFR3c or FGFR4 that form part of the epitope to which certain antibodies provided herein bind. The antibodies can be polyclonal, monoclonal, or can be synthesized in host cells by expressing recombinant DNA.

Fully human antibodies can be prepared as described above by immunizing transgenic animals containing human immunoglobulin loci or by selecting a phage display library that is expressing a repertoire of human antibodies.

The monoclonal antibodies (mAbs) can be produced by a variety of techniques, including conventional monoclonal antibody methodology, e.g., the standard somatic cell hybridization technique of Kohler and Milstein, (1975) *Nature* 256:495. Alternatively, other techniques for producing monoclonal antibodies can be employed, for example, the viral or oncogenic transformation of B-lymphocytes. One suitable animal system for preparing hybridomas is the murine system, which is a very well established procedure. Immunization protocols and techniques for isolation of immunized splenocytes for fusion are known in the art. For such procedures, B cells from immunized mice are fused with a suitable immortalized fusion partner, such as a murine myeloma cell line. If desired, rats or other mammals besides can be immunized instead of mice and B cells from such animals can be fused with the murine myeloma cell line to form hybridomas. Alternatively, a myeloma cell line from a source other than mouse can be used. Fusion procedures for making hybridomas also are well known. SLAM technology can also be employed in the production of antibodies.

The single chain antibodies that are provided can be formed by linking heavy and light chain variable domain (Fv region) fragments via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain. Such single-chain Fvs (scFvs) can be prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides (V_L and V_H). The resulting polypeptides can fold back on themselves to form antigen-binding monomers, or they can form multimers (e.g., dimers, trimers, or tetramers), depending on the length of a flexible linker between the two variable domains (Kortt et al., (1997) *Prot. Eng.* 10:423; Kortt et al., (2001) *Biomol. Eng.* 18:95-108). By combining different V_L and V_H-comprising polypeptides, one can form multimeric scFvs that bind to different epitopes (Kriangkum et al., (2001) *Biomol. Eng.* 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Pat. No. 4,946,778; Bird, (1988) *Science* 242:423; Huston et al., (1988) *Proc. Natl. Acad. Sci. U.S.A.* 85:5879; Ward et al., (1989) *Nature* 334:544, de Graaf et al., (2002) *Methods Mol. Biol.* 178:379-387. Single chain antibodies derived from antibodies provided herein include, but are not limited to scFvs comprising the variable domain combinations of the heavy and light chain variable regions depicted in Table 2, or combinations of light and heavy chain variable domains which include CDRs depicted in Tables 3 and 4.

Antibodies provided herein that are of one subclass can be changed to antibodies from a different subclass using subclass switching methods. Thus, IgG antibodies can be derived from an IgM antibody, for example, and vice versa. Such techniques allow the preparation of new antibodies that possess the antigen binding properties of a given antibody (the parent antibody), but also exhibit biological properties associated with an antibody isotype or subclass different from that of the parent antibody. Recombinant DNA techniques can be employed. Cloned DNA encoding particular antibody polypeptides can be employed in such procedures, e.g., DNA encoding the constant domain of an antibody of the desired isotype. See, e.g., Lantto et al., (2002) *Methods Mol. Biol.* 178:303-316.

Accordingly, the antibodies that are provided include those comprising, for example, the variable domain combinations described, supra., having a desired isotype (for example, IgA, IgG1, IgG2, IgG3, IgG4, IgE, and IgD) as well as Fab or $F(ab')_2$ fragments thereof. Moreover, if an IgG4 is desired, it can also be desired to introduce a point mutation (CPSCP->CPPCP (SEQ ID NOS 380-381, respectively, in order of appearance)) in the hinge region as described in Bloom et al., (1997) *Protein Science* 6:407, incorporated by reference herein) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies.

Moreover, techniques for deriving antibodies having different properties (i.e., varying affinities for the antigen to which they bind) are also known. One such technique, referred to as chain shuffling, involves displaying immunoglobulin variable domain gene repertoires on the surface of filamentous bacteriophage, often referred to as phage display. Chain shuffling has been used to prepare high affinity antibodies to the hapten 2-phenyloxazol-5-one, as described by Marks et al., (1992) *BioTechnology* 10:779.

Conservative modifications can be made to the heavy and light chain variable regions described in Table 2, or the CDRs described in Tables 3A and 3B, 4A and 4B, and Table 6C, infra (and corresponding modifications to the encoding nucleic acids) to produce an antigen binding protein having functional and biochemical characteristics. Methods for achieving such modifications are described above.

Antigen binding proteins that specifically bind one or more of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be further modified in various ways. For example, if they are to be used for therapeutic purposes, they can be conjugated with polyethylene glycol (PEGylated) to prolong the serum half-life or to enhance protein delivery. Alternatively, the V region of the subject antibodies or fragments thereof can be fused with the Fc region of a different antibody molecule. The Fc region used for this purpose can be modified so that it does not bind complement, thus reducing the likelihood of inducing cell lysis in the patient when the fusion protein is used as a therapeutic agent. In addition, the subject antibodies or functional fragments thereof can be conjugated with human serum albumin to enhance the serum half-life of the antibody or fragment thereof. Another useful fusion partner for the antigen binding proteins or fragments thereof is transthyretin (TTR). TTR has the capacity to form a tetramer, thus an antibody-TTR fusion protein can form a multivalent antibody which can increase its binding avidity.

Alternatively, substantial modifications in the functional and/or biochemical characteristics of the antigen binding proteins described herein can be achieved by creating substitutions in the amino acid sequence of the heavy and light chains that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulkiness of the side chain. A "conservative amino acid substitution" can involve a substitution of a native amino acid residue with a normative residue that has little or no effect on the polarity or charge of the amino acid residue at that position. See, Table 5, supra. Furthermore, any native residue in the polypeptide can also be substituted with alanine, as has been previously described for alanine scanning mutagenesis.

Amino acid substitutions (whether conservative or non-conservative) of the subject antibodies can be implemented by those skilled in the art by applying routine techniques. Amino acid substitutions can be used to identify important residues of the antibodies provided herein, or to increase or decrease the affinity of these antibodies for one or more of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 or for modifying the binding affinity of other antigen-binding proteins described herein.

Methods of Expressing Antigen Binding Proteins

Expression systems and constructs in the form of plasmids, expression vectors, transcription or expression cassettes that comprise at least one polynucleotide as described above are also provided herein, as well host cells comprising such expression systems or constructs.

The antigen binding proteins provided herein can be prepared by any of a number of conventional techniques. For example, antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be produced by recombinant expression systems, using any technique known in the art. See, e.g., Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses, Kennet et al. (eds.) Plenum Press, New York (1980); and Antibodies: A Laboratory Manual, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1988).

Antigen binding proteins can be expressed in hybridoma cell lines (e.g., in particular antibodies can be expressed in hybridomas) or in cell lines other than hybridomas. Expression constructs encoding the antibodies can be used to transform a mammalian, insect or microbial host cell. Transformation can be performed using any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus or bacteriophage and transducing a host cell with the construct by transfection procedures known in the art, as exemplified by U.S. Pat. Nos. 4,399,216; 4,912,040; 4,740,461; 4,959,455. The optimal transformation procedure used will depend upon which type of host cell is being transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include, but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, mixing nucleic acid with positively-charged lipids, and direct microinjection of the DNA into nuclei.

Recombinant expression constructs typically comprise a nucleic acid molecule encoding a polypeptide comprising one or more of the following: one or more CDRs provided herein; a light chain constant region; a light chain variable region; a heavy chain constant region (e.g., C_H1, C_H2 and/or

C_H3); and/or another scaffold portion of an antigen binding protein. These nucleic acid sequences are inserted into an appropriate expression vector using standard ligation techniques. In one embodiment, the heavy or light chain constant region is appended to the C-terminus of the anti-β-Klotho, -FGFR1c, -FGFR2c, -FGFR3c, -FGFR4, or β-Klotho and FGFR1c-specific heavy or light chain variable region and is ligated into an expression vector. The vector is typically selected to be functional in the particular host cell employed (i.e., the vector is compatible with the host cell machinery, permitting amplification and/or expression of the gene can occur). In some embodiments, vectors are used that employ protein-fragment complementation assays using protein reporters, such as dihydrofolate reductase (see, for example, U.S. Pat. No. 6,270,964, which is hereby incorporated by reference). Suitable expression vectors can be purchased, for example, from Invitrogen Life Technologies or BD Biosciences (formerly "Clontech"). Other useful vectors for cloning and expressing the antibodies and fragments include those described in Bianchi and McGrew, (2003) *Biotech. Biotechnol. Bioeng.* 84:439-44, which is hereby incorporated by reference. Additional suitable expression vectors are discussed, for example, in *Methods Enzymol., vol.* 185 (D. V. Goeddel, ed.), 1990, New York: Academic Press.

Typically, expression vectors used in any of the host cells will contain sequences for plasmid maintenance and for cloning and expression of exogenous nucleotide sequences. Such sequences, collectively referred to as "flanking sequences" in certain embodiments will typically include one or more of the following nucleotide sequences: a promoter, one or more enhancer sequences, an origin of replication, a transcriptional termination sequence, a complete intron sequence containing a donor and acceptor splice site, a sequence encoding a leader sequence for polypeptide secretion, a ribosome binding site, a polyadenylation sequence, a polylinker region for inserting the nucleic acid encoding the polypeptide to be expressed, and a selectable marker element. Each of these sequences is discussed below.

Optionally, the vector can contain a "tag"-encoding sequence, i.e., an oligonucleotide molecule located at the 5' or 3' end of an antigen binding protein coding sequence; the oligonucleotide sequence encodes polyHis (such as hexaHis (SEQ ID NO: 382)), or another "tag" such as FLAG, HA (hemaglutinin influenza virus), or myc, for which commercially available antibodies exist. This tag is typically fused to the polypeptide upon expression of the polypeptide, and can serve as a means for affinity purification or detection of the antigen binding protein from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies against the tag as an affinity matrix. Optionally, the tag can subsequently be removed from the purified antigen binding protein by various means such as using certain peptidases for cleavage.

Flanking sequences can be homologous (i.e., from the same species and/or strain as the host cell), heterologous (i.e., from a species other than the host cell species or strain), hybrid (i.e., a combination of flanking sequences from more than one source), synthetic or native. As such, the source of a flanking sequence can be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence is functional in, and can be activated by, the host cell machinery.

Flanking sequences useful in the vectors can be obtained by any of several methods well known in the art. Typically, flanking sequences useful herein will have been previously identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In some cases, the full nucleotide sequence of a flanking sequence can be known. Here, the flanking sequence can be synthesized using the methods described herein for nucleic acid synthesis or cloning.

Whether all or only a portion of the flanking sequence is known, it can be obtained using polymerase chain reaction (PCR) and/or by screening a genomic library with a suitable probe such as an oligonucleotide and/or flanking sequence fragment from the same or another species. Where the flanking sequence is not known, a fragment of DNA containing a flanking sequence can be isolated from a larger piece of DNA that can contain, for example, a coding sequence or even another gene or genes. Isolation can be accomplished by restriction endonuclease digestion to produce the proper DNA fragment followed by isolation using agarose gel purification, Qiagen® column chromatography (Chatsworth, Calif.), or other methods known to the skilled artisan. The selection of suitable enzymes to accomplish this purpose will be readily apparent to one of ordinary skill in the art.

An origin of replication is typically a part of those prokaryotic expression vectors purchased commercially, and the origin aids in the amplification of the vector in a host cell. If the vector of choice does not contain an origin of replication site, one can be chemically synthesized based on a known sequence, and ligated into the vector. For example, the origin of replication from the plasmid pBR322 (New England Biolabs, Beverly, Mass.) is suitable for most gram-negative bacteria, and various viral origins (e.g., SV40, polyoma, adenovirus, vesicular stomatitus virus (VSV), or papillomaviruses such as HPV or BPV) are useful for cloning vectors in mammalian cells. Generally, the origin of replication component is not needed for mammalian expression vectors (for example, the SV40 origin is often used only because it also contains the virus early promoter).

A transcription termination sequence is typically located 3' to the end of a polypeptide coding region and serves to terminate transcription. Usually, a transcription termination sequence in prokaryotic cells is a G-C rich fragment followed by a poly-T sequence. While the sequence is easily cloned from a library or even purchased commercially as part of a vector, it can also be readily synthesized using methods for nucleic acid synthesis such as those described herein.

A selectable marker gene encodes a protein necessary for the survival and growth of a host cell grown in a selective culture medium. Typical selection marker genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, tetracycline, or kanamycin for prokaryotic host cells; (b) complement auxotrophic deficiencies of the cell; or (c) supply critical nutrients not available from complex or defined media. Specific selectable markers are the kanamycin resistance gene, the ampicillin resistance gene, and the tetracycline resistance gene. Advantageously, a neomycin resistance gene can also be used for selection in both prokaryotic and eukaryotic host cells.

Other selectable genes can be used to amplify the gene that will be expressed. Amplification is the process wherein genes that are required for production of a protein critical for growth or cell survival are reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples of suitable selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and promoterless thymidine kinase genes. Mammalian cell transformants are placed under selection pressure wherein only the transformants are uniquely adapted to survive by virtue of the selectable gene present in the vector. Selection pressure is imposed by culturing the transformed cells under conditions in which the concentration of selection agent in the medium is successively increased, thereby leading to the amplification of both the selectable gene and the DNA that encodes another gene, such as an antigen binding protein that binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. As a result, increased quantities of a polypeptide such as an antigen binding protein are synthesized from the amplified DNA.

A ribosome-binding site is usually necessary for translation initiation of mRNA and is characterized by a Shine-Dalgarno sequence (prokaryotes) or a Kozak sequence (eukaryotes). The element is typically located 3' to the promoter and 5' to the coding sequence of the polypeptide to be expressed.

In some cases, such as where glycosylation is desired in a eukaryotic host cell expression system, one can manipulate the various pre- or pro-sequences to improve glycosylation or yield. For example, one can alter the peptidase cleavage site of a particular signal peptide, or add prosequences, which also can affect glycosylation. The final protein product can have, in the −1 position (relative to the first amino acid of the mature protein), one or more additional amino acids incident to expression, which may not have been totally removed. For example, the final protein product can have one or two amino acid residues found in the peptidase cleavage site, attached to the amino-terminus. Alternatively, use of some enzyme cleavage sites can result in a slightly truncated form of the desired polypeptide, if the enzyme cuts at such area within the mature polypeptide.

Expression and cloning will typically contain a promoter that is recognized by the host organism and operably linked to the molecule encoding an antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Promoters are untranscribed sequences located upstream (i.e., 5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control transcription of the structural gene. Promoters are conventionally grouped into one of two classes: inducible promoters and constitutive promoters. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, such as the presence or absence of a nutrient or a change in temperature. Constitutive promoters, on the other hand, uniformly transcribe a gene to which they are operably linked, that is, with little or no control over gene expression. A large number of promoters, recognized by a variety of potential host cells, are well known. A suitable promoter is operably linked to the DNA encoding heavy chain or light chain comprising an antigen binding protein by removing the promoter from the source DNA by restriction enzyme digestion and inserting the desired promoter sequence into the vector.

Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable promoters for use with mammalian host cells are well known and include, but are not limited to, those obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, retroviruses, hepatitis-B virus, and Simian Virus 40 (SV40). Other suitable mammalian promoters include heterologous mammalian promoters, for example, heat-shock promoters and the actin promoter.

Additional promoters which can be of interest include, but are not limited to: SV40 early promoter (Benoist and Chambon, (1981) *Nature* 290:304-310); CMV promoter (Thornsen et al., (1984) *Proc. Natl. Acad. U.S.A.* 81:659-663); the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., (1980) *Cell* 22:787-797); herpes thymidine kinase promoter (Wagner et al., (1981) *Proc. Natl. Acad. Sci. U.S.A.* 78:1444-1445); promoter and regulatory sequences from the metallothionine gene (Prinster et al., (1982) *Nature* 296:39-42); and prokaryotic promoters such as the beta-lactamase promoter (VIIIa-Kamaroff et al., (1978) *Proc. Natl. Acad. Sci. U.S.A.* 75:3727-3731); or the tac promoter (DeBoer et al., (1983) *Proc. Natl. Acad. Sci. U.S.A.* 80:21-25). Also of interest are the following animal transcriptional control regions, which exhibit tissue specificity and have been utilized in transgenic animals: the elastase I gene control region that is active in pancreatic acinar cells (Swift et al., (1984) *Cell* 38:639-646; Ornitz et al., (1986) *Cold Spring Harbor Symp. Quant. Biol.* 50:399-409; MacDonald, (1987) *Hepatology* 7:425-515); the insulin gene control region that is active in pancreatic beta cells (Hanahan, (1985) *Nature* 315: 115-122); the immunoglobulin gene control region that is active in lymphoid cells (Grosschedl et al., (1984) *Cell* 38:647-658; Adames et al., (1985) *Nature* 318:533-538; Alexander et al., (1987) *Mol. Cell. Biol.* 7:1436-1444); the mouse mammary tumor virus control region that is active in testicular, breast, lymphoid and mast cells (Leder et al., (1986) *Cell* 45:485-495); the albumin gene control region that is active in liver (Pinkert et al., (1987) *Genes and Devel.* 1:268-276); the alpha-feto-protein gene control region that is active in liver (Krumlauf et al., (1985) *Mol. Cell. Biol.* 5:1639-1648; Hammer et al., (1987) *Science* 253:53-58); the alpha 1-antitrypsin gene control region that is active in liver (Kelsey et al., (1987) *Genes and Devel.* 1:161-171); the beta-globin gene control region that is active in myeloid cells (Mogram et al., (1985) *Nature* 315:338-340; Kollias et al., (1986) *Cell* 46:89-94); the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain (Readhead et al., (1987) *Cell* 48:703-712); the myosin light chain-2 gene control region that is active in skeletal muscle (Sani, (1985) *Nature* 314:283-286); and the gonadotropic releasing hormone gene control region that is active in the hypothalamus (Mason et al., (1986) *Science* 234:1372-1378).

An enhancer sequence can be inserted into the vector to increase transcription of DNA encoding light chain or heavy chain comprising an antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 by higher eukaryotes, e.g., a human antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Enhancers are cis-acting elements of DNA, usually about 10-300 by in length, that act on the promoter to increase transcription. Enhancers are relatively orientation and position independent, having been found at positions both 5' and 3' to the transcription unit. Several enhancer sequences available from mammalian genes are known (e.g., globin, elastase, albumin, alpha-feto-protein and insulin). Typically, however, an enhancer from a virus is used. The SV40 enhancer, the cytomegalovirus early promoter enhancer, the polyoma enhancer, and adenovirus enhancers known in the art are exemplary enhancing elements for the activation of eukaryotic promoters. While an enhancer can be positioned in the vector either 5' or 3' to a coding sequence, it is typically located at a site 5' from the promoter. A sequence encoding an appropriate native or heterologous signal sequence (leader sequence or signal peptide) can be incorporated into an expression vector, to promote extracellular secretion of the antibody. The choice of signal peptide or leader depends on the type of host cells in which the antibody is to be produced, and a heterologous signal sequence can replace the native signal sequence. Examples of signal peptides that are functional in mammalian host cells include the following: the signal sequence for interleukin-7 (IL-7) described in U.S. Pat. No. 4,965,195; the signal sequence for interleukin-2 receptor described in Cosman et al., (1984) *Nature* 312:768; the interleukin-4 receptor signal peptide described in EP Patent No. 0367 566; the type I interleukin-1 receptor signal peptide described in U.S. Pat. No. 4,968,607; the type II interleukin-1 receptor signal peptide described in EP Patent No. 0 460 846.

The expression vectors that are provided can be constructed from a starting vector such as a commercially available vector. Such vectors can but need not contain all of the desired flanking sequences. Where one or more of the flanking sequences described herein are not already present in the vector, they can be individually obtained and ligated into the vector. Methods used for obtaining each of the flanking sequences are well known to one skilled in the art.

After the vector has been constructed and a nucleic acid molecule encoding light chain, a heavy chain, or a light chain and a heavy chain comprising an antigen binding protein that specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 has been inserted into the proper site of the vector, the completed vector can be inserted into a suitable host cell for amplification and/or polypeptide expression. The transformation of an expression vector for an antigen binding protein into a selected host cell can be accomplished by well known methods including transfection, infection, calcium phosphate co-precipitation, electroporation, microinjection, lipofection, DEAE-dextran mediated transfection, or other known techniques. The method selected will in part be a function of the type of host cell to be used. These methods and other suitable methods are well known to the skilled artisan, and are set forth, for example, in Sambrook et al., (2001), supra.

A host cell, when cultured under appropriate conditions, synthesizes an antigen binding protein that can subsequently be collected from the culture medium (if the host cell secretes it into the medium) or directly from the host cell producing it (if it is not secreted). The selection of an appropriate host cell will depend upon various factors, such as desired expression levels, polypeptide modifications that are desirable or necessary for activity (such as glycosylation or phosphorylation) and ease of folding into a biologically active molecule.

Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to, immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), and a number of other cell lines. In certain embodiments, cell lines can be selected through determining which cell lines have high expression levels and constitutively produce antigen binding proteins with desirable binding properties (e.g., the ability to bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4). In another embodiment, a cell line from the B cell lineage that does not make its own antibody but has a capacity to make and secrete a heterologous antibody can be selected. The ability to induce FGF21-like signaling can also form a selection criterion.

Uses of Antigen Binding Proteins for Diagnostic and Therapeutic Purposes

The antigen binding proteins disclosed herein are useful for detecting (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in biological samples and identification of cells or tissues that produce one or more of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. For instance, the antigen binding proteins disclosed herein can be used in diagnostic assays, e.g., binding assays to detect and/or quantify (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 expressed in a tissue or cell. Antigen binding proteins that specifically bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be used in treatment of diseases related to FGF21-like signaling in a patient in need thereof, such as type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome. By forming a signaling complex comprising an antigen binding protein, and (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, the natural in vivo activity of FGF21, which associates with FGFR1c, FGFR2c, FGFR3c, FGFR4 and β-Klotho in vivo to initiate signaling, can be mimicked and/or enchanced, leading to therapeutic effects.

Indications

A disease or condition associated with human FGF21 includes any disease or condition whose onset in a patient is caused by, at least in part, the induction of FGF21-like signaling, which is initiated in vivo by the formation of a complex comprising FGFR1c, FGFR2c, FGFR3c or FGFR4 and β-Klotho and FGF21. The severity of the disease or condition can also be decreased by the induction of FGF21-like signaling. Examples of diseases and conditions that can be treated with the antigen binding proteins include type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome.

The antigen binding proteins described herein can be used to treat type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome, or can be employed as a prophylactic treatment administered, e.g., daily, weekly, biweekly, monthly, bimonthly, biannually, etc to prevent or reduce the frequency and/or severity of symptoms, e.g., elevated plasma glucose levels, elevated triglycerides and cholesterol levels, thereby providing an improved glycemic and cardiovascular risk factor profile.

Diagnostic Methods

The antigen binding proteins described herein can be used for diagnostic purposes to detect, diagnose, or monitor diseases and/or conditions associated with FGFR1c, FGFR2c, FGFR3c, FGFR4, β-Klotho, FGF21 or combinations thereof. Also provided are methods for the detection of the presence of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in a sample using classical immunohistological methods known to those of skill in the art (e.g., Tijssen, 1993, *Practice and Theory of Enzyme Immunoassays*, Vol 15 (Eds R. H. Burdon and P. H. van Knippenberg, Elsevier, Amsterdam); Zola, (1987) *Monoclonal Antibodies: A Manual of Techniques*, pp. 147-158 (CRC Press, Inc.); Jalkanen et al., (1985) *J. Cell. Biol.* 101:976-985; Jalkanen et al., (1987) *J. Cell Biol.* 105:3087-3096). The detection of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be performed in vivo or in vitro.

Diagnostic applications provided herein include use of the antigen binding proteins to detect expression of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and/or binding to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Examples of methods useful in the detection of the presence of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA).

For diagnostic applications, the antigen binding protein typically will be labeled with a detectable labeling group. Suitable labeling groups include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent groups (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic groups (e.g., horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, the labeling group is coupled to the antigen binding protein via spacer arms of various lengths to reduce potential steric hindrance. Various methods for labeling proteins are known in the art and can be used.

In another aspect, an antigen binding protein can be used to identify a cell or cells that express (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In a specific embodiment, the antigen binding protein is labeled with a labeling group and the binding of the labeled antigen binding protein to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 is detected. In a further specific embodiment, the binding of the antigen binding protein to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 detected in vivo. In a further specific embodiment, the antigen binding protein is isolated and measured using techniques known in the art. See, for example, *Harlow and Lane*, (1988) *Antibodies: A Laboratory Manual*, New York: Cold Spring Harbor (ed. 1991 and periodic supplements); *John E. Coligan, ed*., (1993) *Current Protocols In Immunology* New York: John Wiley & Sons.

Another aspect provides for detecting the presence of a test molecule that competes for binding to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with the antigen binding proteins provided, as disclosed herein. An example of one such assay could involve detecting the amount of free antigen binding protein in a solution containing an amount of one or more of (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in the presence or absence of the test molecule. An increase in the amount of free antigen binding protein (i.e., the antigen binding protein not bound to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4) would indicate that the test molecule is capable of competing for binding to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with the antigen binding protein. In one embodiment, the antigen binding protein is labeled with a labeling group. Alternatively, the test molecule is labeled and the amount of free test molecule is monitored in the presence and absence of an antigen binding protein.

Methods of Treatment: Pharmaceutical Formulations and Routes of Administration

Methods of using the antigen binding proteins are also provided. In some methods, an antigen binding protein is provided to a patient. The antigen binding protein induces FGF21-like signaling.

Pharmaceutical compositions that comprise a therapeutically effective amount of one or a plurality of the antigen binding proteins and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, and/or adjuvant are also provided. In addition, methods of treating a patient by administering such pharmaceutical composition are included. The term “patient” includes human patients.

Acceptable formulation materials are nontoxic to recipients at the dosages and concentrations employed. In specific embodiments, pharmaceutical compositions comprising a therapeutically effective amount of human antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 are provided.

In certain embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed. In certain embodiments, the pharmaceutical composition can contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrins); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as Pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. See, *Remington's Pharmaceutical Sciences,* 18th Edition, (A. R. Gennaro, ed.), 1990, Mack Publishing Company.

In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, *Remington's Pharmaceutical Sciences*, supra. In certain embodiments, such compositions can influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the antigen binding proteins disclosed. In certain embodiments, the primary vehicle or carrier in a pharmaceutical composition can be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier can be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In specific embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, and can further include sorbitol or a suitable substitute. In certain embodiments, compositions comprising antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (*Remington's Pharmaceutical Sciences*, supra) in the form of a lyophilized cake or an aqueous solution. Further, in certain embodiments, antigen binding protein that bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be formulated as a lyophilizate using appropriate excipients such as sucrose.

The pharmaceutical compositions can be selected for parenteral delivery. Alternatively, the compositions can be selected for inhalation or for delivery through the digestive tract, such as orally. Preparation of such pharmaceutically acceptable compositions is within the skill of the art.

The formulation components are present preferably in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

When parenteral administration is contemplated, the therapeutic compositions can be provided in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired antigen binding protein in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the antigen binding protein is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that can provide controlled or sustained release of the product which can be delivered via depot injection. In certain embodiments, hyaluronic acid can also be used, which can have the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices can be used to introduce the desired antigen binding protein.

Certain pharmaceutical compositions are formulated for inhalation. In some embodiments, antigen binding proteins that bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 are formulated as a dry, inhalable powder. In specific embodiments, antigen binding protein inhalation solutions can also be formulated with a propellant for aerosol delivery. In certain embodiments, solutions can be nebulized. Pulmonary administration and formulation methods therefore are further described in International Patent Application No. PCT/US94/001875, which is incorporated by reference and describes pulmonary delivery of chemically modified proteins. Some formulations can be administered orally. Antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are administered in this fashion can be formulated with or without carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. In certain embodiments, a capsule can be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of an antigen binding protein. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders can also be employed.

Some pharmaceutical compositions comprise an effective quantity of one or a plurality of human antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in a mixture with non-toxic excipients that are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions can be prepared in unit-dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See, for example, International Patent Application No. PCT/US93/00829, which is incorporated by reference and describes controlled release of porous polymeric microparticles for delivery of pharmaceutical compositions. Sustained-release preparations can include semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained release matrices can include polyesters, hydrogels, polylactides (as disclosed in U.S. Pat. No. 3,773,919 and European Patent Application Publication No. EP 058481, each of which is incorporated by reference), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., 1983, *Biopolymers* 2:547-556), poly (2-hydroxyethyl-inethacrylate) (Langer et al., 1981, *J. Biomed. Mater. Res.* 15:167-277 and Langer, 1982, *Chem. Tech.* 12:98-105), ethylene vinyl acetate (Langer et al., 1981, supra) or poly-D(−)-3-hydroxybutyric acid (European Patent Application Publication No. EP 133,988). Sustained release compositions can also include liposomes that can be prepared by any of several methods known in the art. See, e.g., Eppstein et al., 1985, *Proc. Natl. Acad. Sci. U.S.A.* 82:3688-3692; European Patent Application Publication Nos. EP 036,676; EP 088,046 and EP 143,949, incorporated by reference.

Pharmaceutical compositions used for in vivo administration are typically provided as sterile preparations. Sterilization can be accomplished by filtration through sterile filtration membranes. When the composition is lyophilized, sterilization using this method can be conducted either prior to or following lyophilization and reconstitution. Compositions for parenteral administration can be stored in lyophilized form or in a solution. Parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

In certain embodiments, cells expressing a recombinant antigen binding protein as disclosed herein is encapsulated for delivery (see, *Invest. Ophthalmol Vis Sci* (2002) 43:3292-3298 and *Proc. Natl. Acad. Sciences USA* (2006) 103:3896-3901).

In certain formulations, an antigen binding protein has a concentration of at least 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 50 mg/ml, 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, 100 mg/ml or 150 mg/ml. Some formulations contain a buffer, sucrose and polysorbate. An example of a formulation is one containing 50-100 mg/ml of antigen binding protein, 5-20 mM sodium acetate, 5-10% w/v sucrose, and 0.002-0.008% w/v polysorbate. Certain, formulations, for instance, contain 65-75 mg/ml of an antigen binding protein in 9-11 mM sodium acetate buffer, 8-10% w/v sucrose, and 0.005-0.006% w/v polysorbate. The pH of certain such formulations is in the range of 4.5-6. Other formulations have a pH of 5.0-5.5 (e.g., pH of 5.0, 5.2 or 5.4).

Once the pharmaceutical composition has been formulated, it can be stored in sterile vials as a solution, suspension, gel, emulsion, solid, crystal, or as a dehydrated or lyophilized powder. Such formulations can be stored either in a ready-to-use form or in a form (e.g., lyophilized) that is reconstituted prior to administration. Kits for producing a single-dose administration unit are also provided. Certain kits contain a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments, kits containing single and multi-chambered pre-filled syringes (e.g., liquid syringes and lyosyringes) are provided. The therapeutically effective amount of an antigen binding protein-containing pharmaceutical composition to be employed will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will vary depending, in part, upon the molecule delivered, the indication for which the antigen binding protein is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect.

A typical dosage can range from about 1 μg/kg to up to about 30 mg/kg or more, depending on the factors mentioned above. In specific embodiments, the dosage can range from 10 μg/kg up to about 30 mg/kg, optionally from 0.1 mg/kg up to about 30 mg/kg, alternatively from 0.3 mg/kg up to about 20 mg/kg. In some applications, the dosage is from 0.5 mg/kg to 20 mg/kg. In some instances, an antigen binding protein is dosed at 0.3 mg/kg, 0.5 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, or 20 mg/kg. The dosage schedule in some treatment regimes is at a dose of 0.3 mg/kg qW, 0.5 mg/kg qW, 1 mg/kg qW, 3 mg/kg qW, 10 mg/kg qW, or 20 mg/kg qW.

Dosing frequency will depend upon the pharmacokinetic parameters of the particular antigen binding protein in the formulation used. Typically, a clinician administers the composition until a dosage is reached that achieves the desired effect. The composition can therefore be administered as a single dose, or as two or more doses (which can but need not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Appropriate dosages can be ascertained through use of appropriate dose-response data. In certain embodiments, the antigen binding proteins can be administered to patients throughout an extended time period. Chronic administration of an antigen binding protein minimizes the adverse immune or allergic response commonly associated with antigen binding proteins that are not fully human, for example an antibody raised against a human antigen in a non-human animal, for example, a non-fully human antibody or non-human antibody produced in a non-human species.

The route of administration of the pharmaceutical composition is in accord with known methods, e.g., orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, intraocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. In certain embodiments, the compositions can be administered by bolus injection or continuously by infusion, or by implantation device.

The composition also can be administered locally via implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or encapsulated. In certain embodiments, where an implantation device is used, the device can be implanted into any suitable tissue or organ, and delivery of the desired molecule can be via diffusion, timed-release bolus, or continuous administration.

It also can be desirable to use antigen binding protein pharmaceutical compositions ex vivo. In such instances, cells, tissues or organs that have been removed from the patient are exposed to antigen binding protein pharmaceutical compositions after which the cells, tissues and/or organs are subsequently implanted back into the patient.

In particular, antigen binding proteins that specifically bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be delivered by implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptide. In certain embodiments, such cells can be animal or human cells, and can be autologous, heterologous, or xenogeneic. In certain embodiments, the cells can be immortalized. In other embodiments, in order to decrease the chance of an immunological response, the cells can be encapsulated to avoid infiltration of surrounding tissues. In further embodiments, the encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

Combination Therapies

In another aspect, the present disclosure provides a method of treating a subject for diabetes with a therapeutic antigen binding protein of the present disclosure, such as the fully human therapeutic antibodies described herein, together with one or more other treatments. In one embodiment, such a combination therapy achieves an additive or synergistic effect. The antigen binding proteins can be administered in combination with one or more of the type 2 diabetes or obesity treatments currently available. These treatments for diabetes include biguanide (metaformin), and sulfonylureas (such as glyburide, glipizide). Additional treatments directed at maintaining glucose homeostasis include PPAR gamma agonists (pioglitazone, rosiglitazone); glinides (meglitinide, repaglinide, and nateglinide); DPP-4 inhibitors (Januvia® and Onglyza®) and alpha glucosidase inhibitors (acarbose, voglibose).

Additional combination treatments for diabetes include injectable treatments such as insulin and incretin mimetics (Byetta®, Exenatide®), other GLP-1 (glucagon-like peptide) analogs such as liraglutide, other GLP-1R agonists and Symlin® (pramlintide).

Additional combination treatments directed at weight loss include Meridia® and Xenical®.

EXAMPLES

The following examples, including the experiments conducted and the results achieved, are provided for illustrative purposes only and are not to be construed as limiting.

Example 1

Preparation of FGFR1c Over Expressing Cells for Use as an Antigen

Nucleic acid sequences encoding the full length human FGFR1c polypepetide (SEQ ID NO:4; FIGS. **1A-1B**) and a separate sequence encoding the full length human β-Klotho polypeptide (SEQ ID NO:7; FIGS. **2A-2C**) were subcloned into suitable mammalian cell expression vectors (e.g., pcDNA3.1 Zeo, pcDNA3.1 Hyg (Invitrogen, Carlsbad, Calif.) or pDSRα20. The pDSRα20 vector contains SV40 early promoter/enhancer for expressing the gene of interest and a mouse DHFR expression cassette for selection in CHO DHFR (−) host cells such as AM1 CHO (a derivative of DG44, CHO DHFR (−)).

AM-1 CHO cells were seeded at 1.5×10^6 cells per 100 mm dish. After 24 hours, the cells were co-transfected with linearized DNAs of pDSRα20/huFGFR1c and pDSRα20/huβ-Klotho with FuGene6 (Roche Applied Science). The transfected cells were trypsinized 2 days after transfection and seeded into CHO DHFR selective growth medium containing 10% dialyzed FBS and without hypoxanthine/thymidine supplement. After 2 weeks, the resulting transfected colonies were trypsinized and pooled.

HEK293T cells were transfected with the full length huFGFR1c and huβ-Klotho in pcDNA3.1 series or pTT14 (an expression vector developed by Durocher, NRCC, with CMV promoter and EBV ori, similar to pTT5 and a puromycin selection marker) based vector and selected with the corresponding drugs following similar procedure as for the CHO transfection and selection.

The FGF21R (i.e., FGFR1c and βKlotho) transfected AM1 CHO or 293T cell pools were sorted repeatedly using Alexa 647-labeled FGF21. As a cell-surface staining reagent, FGF21 was labeled with Alexa 647-NHS followed the method recommended by the manufacturer (Molecular Probes, Inc. Cat A 2006). The Alexa 647-labeled FGF21 showed specific staining of FGF21R receptor expressing cells and not the non-transfected parental cells (FIG. **3**). High expressing cells were collected at the end of the final sorting, expanded and frozen into vials. The AM-1/huFGF21R cells were prepared for immunization and the 293T/huFGF21R cells were used for titering mouse sera by FACS after immunization and in binding screens of the hybridoma supernatants by FMAT (see Example 4).

Example 2

Preparation of a Soluble FGFR1c/β-Klotho Complex for Use as Antigen

Soluble FGF21 receptor constructs were generated in pTT14 or pcDNA3.1 expression vectors. The FGFR1c ECD-Fc construct (SEQ ID NO:362, FIG. **4**) comprises the N-terminal extracellular domain of FGFR1c (amino acid residues #1—374; SEQ ID NO:5) fused to Fc (SEQ ID NO:384). The β-Klotho ECD-Fc construct (SEQ ID NO:363, FIG. **5**) comprises the N-terminal extracellular domain of β-Klotho (amino acid residues #1-996; SEQ ID NO:8) fused to Fc (SEQ ID NO:384).

HEK293 cells (293F, Invitrogen) were transfected with huFGFR1c ECD-Fc/pTT5, huβ-Klotho ECD-Fc/pTT14-puro and dGFP/pcDNA3.1-Neo and selected in the presence of the corresponding drugs followed by repeated FACS sorting based on dGFP expression. Cells were grown in serum-free Dulbecco's Modified Eagle Medium (DMEM) supplemented with nonessential amino acids in HyperFlasks (Corning) for 4 days and conditioned media (CM) harvested for purification.

The 293 CM was concentrated 6 fold and applied to Protein A FF equilibrated in PBS. The protein was eluted with Pierce Gentle Ag/Ab elution buffer. The Protein A pool was dialyzed against 20 mM Tris-HCl, pH 7, 10 mM NaCl and applied to SP HP at pH 7.0. The FGFR1c ECD-Fc was present in the flow-through (FT) and the heterodimer was eluted with linear gradient of 0-0.4 M NaCl, 20 mM Tris-HCl pH 7.0. N-terminus amino acid sequencing verified the purified soluble FGF21R to be a heterodimer composed of (1:1) ratio of FGFR1c ECD-Fc and β-Klotho ECD-Fc. The purified soluble FGF21R-Fc (FIG. **6**) was used as the antigen for immunization.

Example 3

Preparation of Monoclonal Antibodies

Immunizations were conducted using one or more suitable forms of FGF21 receptor antigen, including: (1) cell bound receptor of CHO transfectants expressing full length human FGFR1c and β-Klotho at the cell surface, obtained by transfecting CHO cells with cDNA encoding a human full length FGFR1c polypeptide of SEQ ID NO:4 (see also FIGS. **1***a-b*) and cDNA encoding a human β-Klotho polypeptide of SEQ ID NO:7 (see also FIGS. **2***a-c*); (2) membrane extract from the aforementioned cells expressing the FGF21R receptor complex; or (3) soluble FGF21R receptor obtainable by co-expressing the N-terminal extracellular domain (ECD) of FGFR1c (SEQ ID NO:5; see also FIG. **4**) and the N-terminal extracellular domain (ECD) of β-Klotho (SEQ ID NO:8; see also FIG. **5**) or (4) combinations thereof.

A suitable amount of immunogen (i.e., 10 μgs/mouse of soluble FGF21R or $3-4\times10^6$ cells/mouse of stably transfected CHO cells or 150 μgs/mouse of purified FGF21R membranes prepared from CHO cells stably expressing FGF21R) was used for initial immunization in XenoMouse™ according to the methods disclosed in U.S. patent application Ser. No. 08/759,620, filed Dec. 3, 1996 and International Patent Application Nos. WO 98/24893, and WO 00/76310, the disclosures of which are hereby incorporated by reference. Following the initial immunization, subsequent boost immunizations of immunogen (5 μg/mouse of soluble FGF21R or 1.7×10^6 FGF21R transfected cells/mouse or 75 μgs of purified FGF21R membranes) were administered on a schedule and for the duration necessary to induce a suitable anti-FGF21R titer in the mice. Titers were determined by a suitable method, for example, by enzyme immunoassay, fluorescence activated cell sorting (FACS), or by other methods (including combinations of enzyme immunoassays and FACS).

Animals exhibiting suitable titers were identified, and lymphocytes were obtained from draining lymph nodes and, if necessary, pooled for each cohort. Lymphocytes were dissociated from lymphoid tissue by grinding in a suitable medium (for example, Dulbecco's Modified Eagle Medium; DMEM; obtainable from Invitrogen, Carlsbad, Calif.) to release the cells from the tissues, and suspended in DMEM. B cells were selected and/or expanded using standard methods, and fused with suitable fusion partner, for example, nonsecretory myeloma P3X63Ag8.653 cells (American Type Culture Collection CRL1580; Kearney et al, *J. Immunol.* 123, 1979, 1548-1550), using techniques that were known in the art.

In one suitable fusion method, lymphocytes were mixed with fusion partner cells at a ratio of 1:4. The cell mixture was gently pelleted by centrifugation at 400×g for 4 minutes, the supernatant decanted, and the cell mixture gently mixed (for example, by using a 1 ml pipette). Fusion was induced with PEG/DMSO (polyethylene glycol/dimethyl sulfoxide; obtained from Sigma-Aldrich, St. Louis Mo.; 1 ml per million of lymphocytes). PEG/DMSO was slowly added with gentle agitation over one minute followed, by one minute of mixing. IDMEM (DMEM without glutamine; 2 ml per million of B cells), was then added over 2 minutes with gentle agitation, followed by additional IDMEM (8 ml per million B-cells) which was added over 3 minutes.

The fused cells were pelleted (400×g 6 minutes) and resuspended in 20 ml Selection media (for example, DMEM containing Azaserine and Hypoxanthine [HA] and other supplemental materials as necessary) per million B-cells. Cells were incubated for 20-30 minutes at 37° C. and then resuspended in 200 ml selection media and cultured for three to four days in T175 flasks prior to 96 well plating.

Cells were distributed into 96-well plates using standard techniques to maximize clonality of the resulting colonies. After several days of culture, supernatants were collected and subjected to screening assays as detailed in the examples below, including confirmation of binding to human FGF21 receptor, specificity and/or cross-species reactivity. Positive cells were further selected and subjected to standard cloning and subcloning techniques. Clonal lines were expanded in vitro, and the secreted human antibodies obtained for analysis.

In this manner, mice were immunized with either cells or membranes expressing full length FGF21R cells, or soluble FGF21R extracellular domain, with a range of 11-17 immunizations over a period of approximately one to three and one-half months. Several cell lines secreting FGF21R-specific antibodies were obtained, and the antibodies were further characterized. The sequences thereof are presented herein and in the Sequence Listing, and results of various tests using these antibodies are provided.

Example 4

Selection of Binding Antibodies by FMAT

After 14 days of culture, hybridoma supernatants were screened for FGF21R-specific monoclonal antibodies by Fluorometric Microvolume Assay Technology (FMAT) by screening against either the CHO AM1/huFGF21R cell line or recombinant HEK293 cells that were transfected with human FGF21R and counter-screening against parental CHO or HEK293 cells. Briefly the cells in Freestyle media (Invitrogen) were seeded into 384-well FMAT plates in a volume of 50 μL/well at a density of 4,000 cells/well for the stable transfectants, and at a density of 16,000 cells/well for the parental cells, and cells were incubated overnight at 37° C. 10 μL/well of supernatant was then added, and the plates were incubated for approximately one hour at 4° C., after which 10 μL/well of anti-human IgG-Cy5 secondary antibody was added at a concentration of 2.8 μg/ml (400 ng/ml final concentration). Plates were then incubated for one hour at 4° C., and fluorescence was read using an FMAT Cellular Detection System (Applied Biosystems).

In total, over 3,000 hybridoma supernatants were identified as binding to the FGF21 receptor expressing cells but not to parental cells by the FMAT method. These supernatants were then tested in the FGF21 functional assays as described below.

Example 5

Selection of Antibodies that Induce FGF21-Like Signaling

Experiments were performed to identify functional antibodies that mimic wild-type FGF21 activity (e.g., the ability to induce FGF21-like signaling) using a suitable FGF21 reporter assay. The disclosed FGF21 reporter assay measures activation of FGFR signaling via a MAPK pathway readout. β-Klotho is a co-receptor for FGF21 signaling, and although it is believed not to have any inherent signaling capability due to its very short cytoplasmic domain, it is required for FGF21 to induce signaling through FGFRs.

Example 5.1

ELK-Luciferase Reporter Assay

ELK-luciferase assays were performed using a recombinant human 293T kidney cell or CHO cell system. Specifically, the host cells were engineered to over-express β-Klotho and luciferase reporter constructs. The reporter constructs contain sequences encoding GAL4-ELK1 and 5×UAS-Luc, a luciferase reporter driven by a promoter containing five tandem copies of the Gal4 binding site. Activation of the FGF21 receptor complex in these recombinant reporter cell lines induces intracellular signal transduction, which in turn leads to ERK and ELK phosphorylation. Luciferase activity is regulated by the level of phosphorylated ELK, and is used to indirectly monitor and quantify FGF21 activity.

In one example, CHO cells were transfected sequentially using the Lipofectamine 2000 transfection reagent (Invitrogen) according to the manufacturer's protocol with the receptor constructs expressing β-Klotho, FGFR1c and the reporter plasmids: 5× Gal4-Luciferase (minimal TK promoter with 5×Gal4 binding sites upstream of luciferase) and Gal4-ELK1. Gal4-ELK1 binds to the Gal4 binding sites and activates transcription when it is phosphorylated by ERK. Luciferase transcription, and thereby the corresponding enzymatic activity in this context is regulated by the level of phosphorylated ELK1, and is used to indirectly monitor and quantify FGF21 activity.

Clone 2E10 was selected as the FGF21 luciferase reporter cell line based on the optimal assay window of 10-20 fold with native FGF21 exhibiting an EC50 in the single nM range.

For the assay, the ELK-luciferase reporter cells were plated in 96 well assay plates, and serum starved overnight. FGF21 or test samples were added for 6 hours at 37 degrees. The plates were then allowed to cool to room temperature and the luciferase activity in the cell lysates was measured with Bright-Glo (Promega).

Example 5.2

ERK-Phosphorylation Assay

Alternative host cell lines specifically L6 (a rat myoblastic cell line) was developed and applied to identify antibodies with FGF21-like signaling activity. The rat L6 cell line is a desirable host cell line for the activity assay because it is known to express minimal levels of endogeneous FGF receptors. The L6 cells do not respond to FGF21 even when transfected with β-Klotho expression vector and therefore provides a cleaner background. (Kurosu et al., (2007) *J. Biol. Chem.* 282, 26687-26695).

L6 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum and penicillin/streptomycin. Cells were transfected with plasmids expressing βKlotho and individual FGFR using the Lipofectamine 2000 transfection reagent (Invitrogen) according to the manufacturer's protocol.

Analysis of FGF signaling in L6 cells was performed as described in the literature (Kurosu et al., (2007) *J. Biol. Chem.* 282, 26687-26695). Cell cultures were collected 10 min after the treatment of FGF21 or test molecules and snap frozen in liquid nitrogen, homogenized in the lysis buffer and subjected to western blot analysis using an anti-phospho-p44/42 MAP kinase (ERK1/2) antibody and an anti-ERK antibody (Cell Signaling). The percent of phosphorylated ERK versus total ERK protein was determined in this way.

In addition, the factor-dependent mouse BaF3 cell-based proliferation assay used frequently for cytokine receptors can also be developed and applied.

Among the hybridoma supernatants tested in the CHO cell (clone 2E10) based human FGF21 ELK-luciferase reporter assay, over 30 were identified as positive (>5% of the activity of FGF21) when compared to 20 nM FGF21 as the positive control. Antibodies were then purified from the conditioned media of the hybridoma cultures of these positives and tested again in the CHO cell based ELK-luciferase reporter assay. (FIG. **7**) showed the representative antibodies in the dose-responsive potency assay with estimated EC50 less than 1 μg/ml (or 6.7 nM). The activities were confirmed in the L6 cell based ERK1/2-phosphrylation assay (FIG. **8**) with EC50 less than 10 nM which is consistent to the ELK-luciferase assay in the CHO stable cell line 2E10.

Example 6

Induction of FGF21-Like Signaling is Specific to the FGFR1c/βKlotho Complex

FGF21 has been reported to signal through multiple receptor complexes including FGFR1c, 2c, 3c and 4 when paired with β-Klotho. The selectivity of the FGF21 agonistic antibodies was tested in the rat myoblastic L6 cells transfected with vectors expressing the respective FGFRs and βKlotho. The results shown in FIG. **9** demonstrate that the activity was mediated selectively and exclusively through FGFR1c and not through FGFR2c, 3c or 4 when they were paired with β-Klotho because no activity was detected on the latter receptors up to 100 nM of the agonistic antibodies. This unique selectivity strongly suggests that the action of these antibodies is β-Klotho-dependent yet it must also involve specifically the FGFR1c component of the signaling complex.

Example 7

Activity in Primary Human Adipocytes

FGF21 stimulates glucose uptake and lipolysis in cultured adipocytes, and adipocytes are considered to be more physiologically relevant than the recombinant reporter cell system.

A panel of the antibodies was shown to exhibit Erk-phosphorylation activity similar to FGF21 in the human adipocyte assay (FIG. **10**) with estimated EC50 less than 10 nM.

Example 8

Competition Binding and Epitope Binning

To compare the similarity of the binding sites of the antibodies on the FGF21 receptor, a series of competition binding experiments were performed and measured by Biacore™. In one example (and as shown in FIG. **11**), two representative agonistic FGF21 receptor antibodies (24H11 and 17D8) and one non-functional FGF21 receptor binding antibodies (1A2.1) were immobilized on the sensor chip surface. Soluble human FGFR1c/β-Klotho ECD-Fc complex or β-Klotho was then captured on the immobilized antibody surfaces. Finally, several of the test FGF21 receptor antibodies were injected individually over the captured soluble human FGF21 receptor or β-Klotho. If the injected antibody recognizes a distinct binding site relative to that recognized by the immobilized antibody, a second binding event will be observed. If the antibodies recognize very similar binding site, no more binding will be observed.

As shown in (FIG. **11**A), there are two distinct yet partially overlapping binding sites for the agonistic antibodies tested. One site is covered by 24H11, 21H2, 18B11.1 and 17C3 (Group A) and the other site covered by 17D8, 12E4 and 18G1 (Group B). The two non-functional antibodies 2G10 and 1A2, bind to different sites from each other and are distinct from the two sites covered by the agonistic antibodies in Group A and B. Other functional antibodies binding to Group A epitope included 20D4, 22H5, 16H7, 40D2 and 46D11. Two other functional antibodies 26H11 and 37D3 were shown by this method to bind the same site covered by the Group B antibodies. In addition, a third binding site for functional antibodies was identified for 39F11, 39F7 and 39G5 (group C) which appeared to be distinct from Group A and B binding sites (FIG. **11**B).

Another Biacore™analysis was carried out with biotinylated-FGF21 immobilized on the sensor ship. 10 nM soluble β-Klotho was then passed over the chip alone or mixed with the individual test antibodies at 100nM. (FIG. **12**) showed that several agonistic antibodies in group A (24H11, 18B11, 17C3) and antibody 12E4 (from group B) competed significantly with FGF21 in binding to soluble β-Klotho whereas the non-functional antibodies 2G10 and 1A2 and several other functional antibodies did not show competition binding with FGF21.

FIG. **11**C summarizes the binning results obtained.

Example 9

Recognition of Native and Denatures Structures

The ability of disclosed antigen binding proteins to recognize denatured and native structures was investigated. The procedure and results were as follows.

Example 9.1

FGF21 Receptor Agonistic Antibodies do not Recognize Denatured Structures, as Shown by FACS

Cell lysates from CHO cells stably expressing FGF21 receptor (FGFR1c and β-Klotho) or CHO parental cells were diluted with sample buffer without beta-mercaptoethanol (non-reducing conditions). 20 μl of cell lysate was loaded per lane on adjacent lanes separated with a molecular weight marker lane on 4-20% SDS-PAGE gels. Following electrophoresis, the gels were blotted onto 0.2μ nitrocellulose filters. The blots were treated with Tris-buffered saline/Triton-X (TBST) plus 5% non-fat milk (blocking buffer) for 30 minutes. The blots were then cut along the molecular weight marker lanes. The strips were then probed with FGF21 receptor agonistic antibodies (12C3, 26H11, 12E4, 21H2, 18B11, or 20D4), and commercial goat anti-murine βKlotho or mouse anti-huFGFR1 (R&D Diagnostics) in TBST/5% milk. Blots were incubated with the antibodies for one hour at room temperature, followed by three washes with TBST+1% milk. The blots were then probed with anti-human or anti-goat IgG-HRP secondary antibodies for 20 min. Blots were given three 15 min. washes with TBST followed by treatment with Pierce Supersignal West Dura developing reagent (1 min.) and exposure to Kodak Biomax X-ray film.

The commercial anti-β-Klotho and anti-FGFR1 antibodies detected the corresponding receptor proteins in the SDS-PAGE indicating they bind to denatured receptor proteins. In contrast, none of the FGF21 receptor agonistic antibodies tested detected the corresponding protein species suggesting they bind to the native conformational epitope distinct from the commercial antibodies which bind to denatured sequences.

Example 9.2

FGF21 Receptor Agonistic Antibodies Bind to Native Receptor Structure, as Shown by FACS

A FACS binding assay was performed with several commercially available FGFR1c and β-Klotho antibodies, and several of the disclosed FGF21 receptor agonistic antibodies. The experiments were performed as follows.

CHO cells stably expressing FGF21 receptor were treated with R&D Systems mouse anti-huFGFR1, goat anti-mu β-Klotho, or FGF21 receptor antibodies 24H11, 17C3, 17D8, 18G1, or 2G10 (1 μg per 1×10^6 cells in 100 μl PBS/0.5% BSA). Cells were incubated with the antibodies at 4° C. followed by two washes with PBS/BSA. Cells were then treated with FITC-labeled secondary antibodies at 4° C. followed by two washes. The cells were resuspended in 1 ml PBS/BSA and antibody binding was analyzed using a FACS Calibur instrument.

Consistent with western blot results, all of the FGF21 receptor agonistic antibodies tested bind well to cell surface FGF21 receptor in FACS whereas the commercial anti-β-Klotho or anti-FGFR1 antibodies did not. This observation further confirmed that the FGF21 receptor agonistic antibodies recognize the native structure whereas the commercial antibodies to the receptor components do not.

Example 10

Arginine Scanning

As described above, antigen binding proteins that bind human FGF21R, e.g., FGFR1c, β-Klotho or both FGFR1c and β-Klotho, were created and characterized. To determine the neutralizing determinants on human FGFR1c and/or β-Klotho that these various antigen binding proteins bound, a number of mutant FGFR1c and/or β-Klotho proteins can be constructed having arginine substitutions at select amino acid residues of human FGFR1c and/or β-Klotho. Arginine scanning is an art-recognized method of evaluating where antibodies, or other proteins, bind to another protein, see, e.g., Nanevicz et al., (1995) *J. Biol. Chem.,* 270:37, 21619-21625 and Zupnick et al., (2006) *J. Biol. Chem.,* 281:29, 20464-20473. In general, the arginine sidechain is positively charged and relatively bulky as compared to other amino acids, which can disrupt antibody binding to a region of the antigen where the mutation is introduced. Arginine scanning is a method that determines if a residue is part of a neutralizing determinant and/or an epitope.

Various amino acids distributed throughout the human FGFR1c and/or β-Klotho extracellular domains can be selected for mutation to arginine. The selection can be biased towards charged or polar amino acids to maximize the possibility of the residue being on the surface and reduce the likelihood of the mutation resulting in misfolded protein. Using standard techniques known in the art, sense and anti-sense oligonucleotides containing the mutated residues can be designed based on criteria provided by Stratagene Quickchange® II protocol kit (Stratagene/Agilent, Santa Clara, Calif.). Mutagenesis of the wild-type (WT) FGFR1c and/or β-Klotho sequences can be performed using a Quickchange® II kit (Stratagene). Chimeric constructs can be engineered to encode a FLAG-histidine tag (six histidines (SEQ ID NO: 382)) on the carboxy terminus of the extracellular domain to facilitate purification via the poly-His tag.

Multiplex analysis using the Bio-Plex®Workstation and software (Bio-Rad®, Hercules, Calif.) can be performed to determine neutralizing determinants on human FGFR1c and/or β-Klotho by analyzing exemplary human FGFR1c and/or β-Klotho mAbs differential binding to argininemutants versus wild-type FGFR1c and/or β-Klotho proteins. Any number of bead codes of pentaHis-coated beads ("penta-His" disclosed as SEQ ID NO: 383) (Qiagen®, Valencia, Calif.) can be used to capture histidine-tagged protein. The bead codes can allow the multiplexing of FGFR1c and/or β-Klotho arginine mutants and wild-type human FGFR1c and/or β-Klotho.

To prepare the beads, 100 ul of wild-type FGFR1c and/or β-Klotho and FGFR1c and/or β-Klotho arginine mutant supernatants from transient expression culture are bound to penta-His-coated beads ("penta-His" disclosed as SEQ ID NO: 383) overnight at 4° C. or 2 hours at room temperature with vigorous shaking. The beads are then washed as per the manufacturer's protocol and the bead set pooled and aliquoted into 2 or 3 columns of a 96-well filter plate (Millipore, Bellerica, Mass., product #MSBVN1250) for duplicate or triplicate assay points, respectively. 100 μl anti-FGFR1c and/or anti-β-Klotho antibodies in 4-fold dilutions are added to the wells, incubated for 1 hour at room temperature, and washed. 100 μl of a 1:100 dilution of PE-conjugated anti-human IgG Fc (Jackson Labs., Bar Harbor, Me., product #109-116-170) is added to each well, incubated for 1 hour at room temperature and washed. Beads are resuspended in 1% BSA, shaken for 3 minutes, and read on the Bio-Plex workstation. Antibody binding to FGFR1c and/or β-Klotho arginine mutant protein is compared to antibody binding to the human FGFR1c and/or β-Klotho wild-type from the same pool. A titration of antibody over approximately a 5 log scale can be performed. Median Fluorescence Intensity (MFI) of FGFR1c and/or β-Klotho arginine mutant proteins can be graphed as a percent of maximum wild-type human FGFR1c and/or β-Klotho signal. Those mutants for which signal from all the antibodies are below a cut-off value, e.g., 30% of wild-type FGFR1c and/or β-Klotho can be deemed to be either of too low a protein concentration on the bead due to poor expression in the transient culture or possibly misfolded and can be excluded from analysis. Mutations (i.e., arginine substitutions) that increase the EC50 for the FGFR1c and/or β-Klotho mAb by a cut-off value, e.g., 3-fold or greater (as calculated by, e.g., GraphPad Prism®) can be considered to have negatively affected FGFR1c and/or β-Klotho mAb binding. Through these methods, neutralizing determinants and epitopes for various FGFR1c and/or β-Klotho antibodies are elucidated.

Example 11

Construction of Chimeric Receptors

In another method of determining the activation determinants on human FGFR1c and/or β-Klotho that these various antigen binding proteins bind, specific chimeric FGFR1c and/or β-Klotho proteins between human and mouse species can be constructed, expressed in transient or stable 293 or CHO cells as described before and tested. For example, a chimeric FGF21 receptor can be constructed comprising native human FGFR1c, FGFR2c, FGFR3c or FGFR4, in one example FGFR1c, paired with chimeric human/mouse β-Klotho in which selected regions or sequences on the human β-Klotho are systematically replaced by the corresponding mouse-specific residues (see, e.g., FIG. **2**A-**2**C). Similarly, native human β-Klotho paired with chimeric human/mouse FGFR1c, FGFR2c, FGFR3c or FGFR4, in one example FGFR1c in which selected regions or sequences on the human FGFR1c are systematically replaced by the corresponding mouse-specific residues (see, e.g., the alignments of FIGS. **1**A-**1**B). The critical sequences involved in the binding and/or activity of the antigen binding proteins can be derived through binding assay or activity measurements described in previous Examples 4, 5, 6 and 7 based on the chimeric FGF21 receptors.

Example 11.1

Construction of Specific Chimeras

Human-mouse β-Klotho chimeras were constructed using the methodology described in Example 14. A schematic of the chimeras constructed is presented in FIG. **29**; summarily, the chimeras generated comprised (from N to C terminus) a fusion of a human β-Klotho sequence fused to a murine β-Klotho sequence fused to a human β-Klotho sequence. Human β-Klotho (SEQ ID NO:8) was used as a framework into which regions of murine β-Klotho (full length sequence shown in SEQ ID NO:468) were inserted. The regions of murine β-Klotho that were inserted were as follows:

```
Murine Residues 82P-520P
                                                     (SEQ ID NO: 470)
PKNFSWGVGTGAFQVEGSWKTDGRGPSIWDRYVYSHLRGVNGTDRSTDSYIFLEKDLL

ALDFLGVSFYQFSISWPRLFPNGTVAAVNAQGLRYYRALLDSLVLRNIEPIVTLYHWDLP

LTLQEEYGGWKNATMIDLFNDYATYCFQTFGDRVKYWITIHNPYLVAWHGFGTGMHA

PGEKGNLTAVYTVGHNLIKAHSKVWHNYDKNFRPHQKGWLSITLGSHWIEPNRTDNM

EDVINCQHSMSSVLGWFANPIHGDGDYPEFMKTGAMIPEFSEAEKEEVRGTADFFAFSF

GPNNFRPSNTVVKMGQNVSLNLRQVLNWIKLEYDDPQILISENGWFTDSYIKTEDTTAIY

MMKNFLNQVLQAIKFDEIRVFGYTAWTLLDGFEWQDAYTTRRGLFYVDFNSEQKERKP

KSSAHYYKQIIQDNGFPLKESTPDMKGRFP

Murine Residues 506F-1043S
                                                     (SEQ ID NO: 471)
FPLKESTPDMKGRFPCDFSWGVTESVLKPEFTVSSPQFTDPHLYVWNVTGNRLLYRVEG

VRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFALDWTSILPTGNLSKVNRQVLRYYR

CVVSEGLKLGVFPMVTLYHPTHSHLGLPLPLLSSGGWLNMNTAKAFQDYAELCFRELG

DLVKLWITINEPNRLSDMYNRTSNDTYRAAHNLMIAHAQVWHLYDRQYRPVQHGAVS

LSLHCDWAEPANPFVDSHWKAAERFLQFEIAWFADPLFKTGDYPSVMKEYIASKNQRG

LSSSVLPRFTAKESRLVKGTVDFYALNHFTTRFVIHKQLNTNRSVADRDVQFLQDITRLS

SPSRLAVTPWGVRKLLAWIRRNYRDRDIYITANGIDDLALEDDQIRKYYLEKYVQEALK

AYLIDKVKIKGYYAFKLTEEKSKPRFGFFTSDFRAKSSVQFYSKLISSSGLPAENRSPACG

QPAEDTDCTICSFLVEKKPLIFFGCCFISTLAVLLSITVFHHQKRRKFQKARNLQNIPLKK

GHSRVFS
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-continued

Murine Residues 1M-193L

(SEQ ID NO: 472)

MKTGCAAGSPGNEWIFFSSDERNTRSRKTMSNRALQRSAVLSAFVLLRAVTGFSGDGK

AIWDKKQYVSPVNPSQLFLYDTFPKNFSWGVGTGAFQVEGSWKTDGRGPSIWDRYVYS

HLRGVNGTDRSTDSYIFLEKDLLALDFLGVSFYQFSISWPRLFPNGTVAAVNAQGLRYY

RALLDSLVLRNIEPIVTL

Murine Residues 82P-302S

(SEQ ID NO: 473)

PKNFSWGVGTGAFQVEGSWKTDGRGPSIWDRYVYSHLRGVNGTDRSTDSYIFLEKDLL

ALDFLGVSFYQFSISWPRLFPNGTVAAVNAQGLRYYRALLDSLVLRNIEPIVTLYHWDLP

LTLQEEYGGWKNATMIDLFNDYATYCFQTFGDRVKYWITIHNPYLVAWHGFGTGMHA

PGEKGNLTAVYTVGHNLIKAHSKVWHNYDKNFRPHQKGWLSITLGS

Murine Residues 194Y-416G

(SEQ ID NO: 474)

YHWDLPLTLQEEYGGWKNATMIDLFNDYATYCFQTFGDRVKYWITIHNPYLVAWHGF

GTGMHAPGEKGNLTAVYTVGHNLIKAHSKVWHNYDKNFRPHQKGWLSITLGSHWIEP

NRTDNMEDVINCQHSMSSVLGWFANPIHGDGDYPEFMKTGAMIPEFSEAEKEEVRGTA

DFFAFSFGPNNFRPSNTVVKMGQNVSLNLRQVLNWIKLEYDDPQILISENG

Murine Residues 302S-506F

(SEQ ID NO: 475)

SHWIEPNRTDNMEDVINCQHSMSSVLGWFANPIHGDGDYPEFMKTGAMIPEFSEAEKEE

VRGTADFFAFSFGPNNFRPSNTVVKMGQNVSLNLRQVLNWIKLEYDDPQILISENGWFT

DSYIKTEDTTAIYMMKNFLNQVLQAIKFDEIRVFGYTAWTLLDGFEWQDAYTTRRGLFY

VDFNSEQKERKPKSSAHYYKQIIQDNGF

Murine Residues 416G-519P

(SEQ ID NO: 476)

GWFTDSYIKTEDTTAIYMMKNFLNQVLQAIKFDEIRVFGYTAWTLLDGFEWQDAYTTR

RGLFYVDFNSEQKERKPKSSAHYYKQIIQDNGFPLKESTPDMKGRF

Murine Residues 507P-632G

(SEQ ID NO: 477)

PLKESTPDMKGRFPCDFSWGVTESVLKPEFTVSSPQFTDPHLYVWNVTGNRLLYRVEGV

RLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFALDWTSILPTGNLSKVNRQVLRYYRC

VVSEGLKLG

Murine Residues 520P-735A

(SEQ ID NO: 478)

PCDFSWGVTESVLKPEFTVSSPQFTDPHLYVWNVTGNRLLYRVEGVRLKTRPSQCTDY

VSIKKRVEMLAKMKVTHYQFALDWTSILPTGNLSKVNRQVLRYYRCVVSEGLKLGVFP

MVTLYHPTHSHLGLPLPLLSSGGWLNMNTAKAFQDYAELCFRELGDLVKLWITINEPNR

LSDMYNRTSNDTYRAAHNLMIAHAQVWHLYDRQYRPVQHGA

Murine Residues 632G-849Q

(SEQ ID NO: 479)

GVFPMVTLYHPTHSHLGLPLPLLSSGGWLNMNTAKAFQDYAELCFRELGDLVKLWITIN

EPNRLSDMYNRTSNDTYRAAHNLMIAHAQVWHLYDRQYRPVQHGAVSLSLHCDWAE

PANPFVDSHWKAAERFLQFEIAWFADPLFKTGDYPSVMKEYIASKNQRGLSSSVLPRFT

AKESRLVKGTVDFYALNHFTTRFVIHKQLNTNRSVADRDVQFLQ

Murine Residues 735A-963S

(SEQ ID NO: 480)

AVSLSLHCDWAEPANPFVDSHWKAAERFLQFEIAWFADPLFKTGDYPSVMKEYIASKN

QRGLSSSVLPRFTAKESRLVKGTVDFYALNHFTTRFVIHKQLNTNRSVADRDVQFLQDIT

-continued

RLSSPSRLAVTPWGVRKLLAWIRRNYRDRDIYITANGIDDLALEDDQIRKYYLEKYVQE

ALKAYLIDKVKIKGYYAFKLTEEKSKPRFGFFTSDFRAKSSVQFYSKLISSS

Murine Residues 1M-81F

(SEQ ID NO: 481)

MKTGCAAGSPGNEWIFFSSDERNTRSRKTMSNRALQRSAVLSAFVLLRAVTGFSGDGK

AIWDKKQYVSPVNPSQLFLYDTF

Murine Residues 82P-193L

(SEQ ID NO: 482)

PKNFSWGVGTGAFQVEGSWKTDGRGPSIWDRYVYSHLRGVNGTDRSTDSYIFLEKDLL

ALDFLGVSFYQFSISWPRLFPNGTVAAVNAQGLRYYRALLDSLVLRNIEPIVTL

The chimeras generated using the murine β-Klotho sequences comprised the following components:

Construct Identifier	Construct SEQ ID NO	N-terminal Human β-Klotho Residues	Mouse β-Klotho Residues	C-terminal Human β-Klotho Residues
huBeta_Klotho(1-81, 523-1044) (muBetaKLOTHO 82-520)		1-81	82-520	523-1044
huBeta_Klotho(1-507) (muBetaKLOTHO 506F-1045S)		1-507	506-1043	
huBeta_Klotho(194-1044) (muBetaKLOTHO 1-L193)			1-193	194-1044
huBeta_Klotho(1-81, 303-1044) (muBetaKLOTHO 82P-302S)		1-81	82-302	303-1044
huBeta_Klotho(1-193, 419-1044) (muBetaKLOTHO Y194-416G)		1-193	194-416	419-1044
huBeta_Klotho(1-301, 509-1044) (muBetaKLOTHO S302-F506)		1-301	302-506	509-1044
huBeta_Klotho(1-417, 522-1044) (muBetaKLOTHO G416-F519)		1-417	416-519	522-1044
huBeta_Klotho(1-507, 635-1044) (muBeta KLOTHO F06-G632)		1-508	507-632	635-1044
huBeta_Klotho(1-521, 738-1044) (muBeta KLOTHO 520P-735A)		1-521	520-735	738-1044
huBeta_Klotho(1-633, 852-1044) (muBeta KLOTHO 632G-849Q)		1-633	632-849	852-1044
huBeta_Klotho(1-736, 967-1044) (muBeta KLOTHO 735A-963S)		1-736	735-963	967-1044
huBeta_Klotho(82-1044)(muBeta KLOTHO 1-81F)			1-81	82-1044
huBeta_Klotho(1-81, 194-1044) (muBeta KLOTHO 82P-193L)		1-81	82-193	194-1044

The generated chimeras comprised the following amino acid sequences:

(i) huBeta_Klotho(1-81, 523-1044)(muBetaKLOTHO 82-520)

(SEQ ID NO: 455)

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFSWGVGTGAFQVEGSW
KTDGRGPSIWDRYVYSHLRGVNGTDRSTDSYIFLEKDLLALDFLGVSFYQ
FSISWPRLFPNGTVAAVNAQGLRYYRALLDSLVLRNIEPIVTLYHWDLPL
TLQEEYGGWKNATMIDLFNDYATYCFQTFGDRVKYWITIHNPYLVAWHGF
GTGMHAPGEKGNLTAVYTVGHNLIKAHSKVWHNYDKNFRPHQKGWLSITL
GSHWIEPNRTDNMEDVINCQHSMSSVLGWFANPIHGDGDYPEFMKTGAMI
PEFSEAEKEEVRGTADFFAFSFGPNNFRPSNTVVKMGQNVSLNLRQVLNW
IKLEYDDPQILISENGWFTDSYIKTEDTTAIYMMKNFLNQVLQAIKFDEI
RVFGYTAWTLLDGFEWQDAYTTRRGLFYVDFNSEQKERKPKSSAHYYKQI
IQDNGFPLKESTPDMKGRFPCDFSWGVTESVLKPESVASSPQFSDPHLYV
WNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFALD
WASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLGLP
EPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDIYN
RSGNDTYGAAHNLLVAHALAWRLYDQQFRPSQRGAVSLSLHADWAEPANP
YADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSSSA
LPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFLQD
ITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDDRL
RKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFKAK

-continued

SSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFLGC
CFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

(ii) huBeta_Klotho(1-507)(muBetaKLOTHO 506F-1045S)
(SEQ ID NO: 456)

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL
ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
QIIRENGFPLKESTPDMKGRFPCDFSWGVTESVLKPEFTVSSPQFTDPHL
YVWNVTGNRLLYRVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFA
LDWTSILPTGNLSKVNRQVLRYYRCVVSEGLKLGVFPMVTLYHPTHSHLG
LPLPLLSSGGWLNMNTAKAFQDYAELCFRELGDLVKLWITINEPNRLSDM
YNRTSNDTYRAAHNLMIAHAQVWHLYDRQYRPVQHGAVSLSLHCDWAEPA
NPFVDSHWKAAERFLQFEIAWFADPLFKTGDYPSVMKEYIASKNQRGLSS
SVLPRFTAKESRLVKGTVDFYALNHFTTRFVIHKQLNTNRSVADRDVQFL
QDITRLSSPSRLAVTPWGVRKLLAWIRRNYRDRDIYITANGIDDLALEDD
QIRKYYLEKYVQEALKAYLIDKVKIKGYYAFKLTEEKSKPRFGFFTSDFR
AKSSVQFYSKLISSSGLPAENRSPACGQPAEDTDCTICSFLVEKKPLIFF
GCCFISTLAVLLSITVFHHQKRRKFQKARNLQNIPLKKGHSRVFS

(iii) huBeta_Klotho(194-1044)(muBetaKLOTHO 1-L193)
(SEQ ID NO: 457)

MKTGCAAGSPGNEWIFFSSDERNTRSRKTMSNRALQRSAVLSAFVLLRAV
TGFSGDGKAIWDKKQYVSPVNPSQLFLYDTFPKNFSWGVGTGAFQVEGSW
KTDGRGPSIWDRYVYSHLRGVNGTDRSTDSYIFLEKDLLALDFLGVSFYQ
FSISWPRLFPNGTVAAVNAQGLRYYRALLDSLVLRNIEPIVTLYHWDLPL
ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
QIIRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHL
YVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA
LDWASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLG
LPEPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDI
YNRSGNDTYGAAHNLLVAHALAWRLYDQQFRPSQRGAVSLSLHADWAEPA
NPYADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSS
SALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFL
QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD
RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK
AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

(iv) huBeta_Klotho(1-81, 303-1044)(muBetaKLOTHO 82P-302S)
(SEQ ID NO: 458)

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFSWGVGTGAFQVEGSW
KTDGRGPSIWDRYVYSHLRGVNGTDRSTDSYIFLEKDLLALDFLGVSFYQ
FSISWPRLFPNGTVAAVNAQGLRYYRALLDSLVLRNIEPIVTLYHWDLPL
TLQEEYGGWKNATMIDLFNDYATYCFQTFGDRVKYWITIHNPYLVAWHGF
GTGMHAPGEKGNLTAVYTVGHNLIKAHSKVWHNYDKNFRPHQKGWLSITL
GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
QIIRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHL
YVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA
LDWASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLG
LPEPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDI
YNRSGNDTYGAAHNLLVAHALAWRLYDQQFRPSQRGAVSLSLHADWAEPA
NPYADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSS
SALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFL
QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD
RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK
AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

(v) huBeta_Klotho(1-193, 419-1044)(muBetaKLOTHO Y194-416G)
(SEQ ID NO: 459)

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL

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TLQEEYGGWKNATMIDLFNDYATYCFQTFGDRVKYWITIHNPYLVAWHGF
GTGMHAPGEKGNLTAVYTVGHNLIKAHSKVWHNYDKNFRPHQKGWLSITL
GSHWIEPNRTDNMEDVINCQHSMSSVLGWFANPIHGDGDYPEFMKTGAMI
PEFSEAEKEEVRGTADFFAFSFGPNNFRPSNTVVKMGQNVSLNLRQVLNW
IKLEYDDPQILISENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLDEI
RVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYKQI
IRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHLYV
WNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFALD
WASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLGLP
EPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDIYN
RSGNDTYGAAHNLLVAHALAWRLYDQQFRPSQRGAVSLSLHADWAEPANP
YADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSSSA
LPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFLQD
ITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDDRL
RKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFKAK
SSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFLGC
CFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

(vi) huBeta_Klotho(1-301, 509-1044)(muBetaKLOTHO S302-F506)
(SEQ ID NO: 460)

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL
ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
GSHWIEPNRTDNMEDVINCQHSMSSVLGWFANPIHGDGDYPEFMKTGAMI
PEFSEAEKEEVRGTADFFAFSFGPNNFRPSNTVVKMGQNVSLNLRQVLNW
IKLEYDDPQILISENGWFTDSYIKTEDTTAIYMMKNFLNQVLQAIKFDEI
RVFGYTAWTLLDGFEWQDAYTTRRGLFYVDFNSEQKERKPKSSAHYYKQI
IQDNGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHLYV
WNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFALD
WASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLGLP
EPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDIYN
RSGNDTYGAAHNLLVAHALAWRLYDQQFRPSQRGAVSLSLHADWAEPANP
YADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSSSA
LPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFLQD
ITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDDRL
RKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFKAK
SSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFLGC
CFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

(vii) huBeta_Klotho(1-417, 522-1044)(muBetaKLOTHO G416-F519)
(SEQ ID NO: 461)

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL
ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
NWIKLEYNNPRILIAENGWFTDSYIKTEDTTAIYMMKNFLNQVLQAIKFD
EIRVFGYTAWTLLDGFEWQDAYTTRRGLFYVDFNSEQKERKPKSSAHYYK
QIIQDNGFPLKESTPDMKGRFPCDFSWGVTESVLKPESVASSPQFSDPHL
YVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA
LDWASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLG
LPEPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDI
YNRSGNDTYGAAHNLLVAHALAWRLYDQQFRPSQRGAVSLSLHADWAEPA
NPYADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSS
SALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFL
QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD
RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK
AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

(viii) huBeta_Klotho(1-507, 635-1044)(muBeta KLOTHO F06-G632)
(SEQ ID NO: 462)

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL
ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
QIIRENGFPLKESTPDMKGRFPCDFSWGVTESVLKPEFTVSSPQFTDPHL
YVWNVTGNRLLYRVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFA
LDWTSILPTGNLSKVNRQVLRYYRCVVSEGLKLGISAMVTLYYPTHAHLG

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LPEPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDI
YNRSGNDTYGAAHNLLVAHALAWRLYDQQFRPSQRGAVSLSLHADWAEPA
NPYADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSS
SALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFL
QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD
RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK
AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

(ix) huBeta_Klotho(1-521, 738-1044)(muBeta KLOTHO 520P-735A)
(SEQ ID NO: 463)

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL
ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
QIIRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPEFTVSSPQFTDPHL
YVWNVTGNRLLYRVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFA
LDWTSILPTGNLSKVNRQVLRYYRCVVSEGLKLGVFPMVTLYHPTHSHLG
LPLPLLSSGGWLNMNTAKAFQDYAELCFRELGDLVKLWITINEPNRLSDM
YNRTSNDTYRAAHNLMIAHAQVWHLYDRQYRPVQHGAVSLSLHADWAEPA
NPYADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSS
SALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFL
QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD
RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK
AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

(x) huBeta_Klotho(1-633, 852-1044)(muBeta KLOTHO 632G-849Q)
(SEQ ID NO: 464)

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL
ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
QIIRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHL
YVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA
LDWASVLPTGNLSAVNRQALRYYRCVVSEGLKLGVFPMVTLYHPTHSHLG
LPLPLLSSGGWLNMNTAKAFQDYAELCFRELGDLVKLWITINEPNRLSDM
YNRTSNDTYRAAHNLMIAHAQVWHLYDRQYRPVQHGAVSLSLHCDWAEPA
NPFVDSHWKAAERFLQFEIAWFADPLFKTGDYPSVMKEYIASKNQRGLSS
SVLPRFTAKESRLVKGTVDFYALNHFTTRFVIHKQLNTNRSVADRDVQFL
QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD
RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK
AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

(xi) huBeta_Klotho(1-736, 967-1044)(muBeta KLOTHO 735A-963S)
(SEQ ID NO: 465)

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSW
KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL
ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
QIIRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHL
YVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA
LDWASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLG
LPEPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDI
YNRSGNDTYGAAHNLLVAHALAWRLYDQQFRPSQRGAVSLSLHCDWAEPA
NPFVDSHWKAAERFLQFEIAWFADPLFKTGDYPSVMKEYIASKNQRGLSS
SVLPRFTAKESRLVKGTVDFYALNHFTTRFVIHKQLNTNRSVADRDVQFL
QDITRLSSPSRLAVTPWGVRKLLAWIRRNYRDRDIYITANGIDDLALEDD
QIRKYYLEKYVQEALKAYLIDKVKIKGYYAFKLTEEKSKPRFGFFTSDFR
AKSSVQFYSKLISSSGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

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(xii)  huBeta_Klotho(82-1044)(muBeta KLOTHO 1-81F)
                                                         (SEQ ID NO: 466)
       MKTGCAAGSPGNEWIFFSSDERNTRSRKTMSNRALQRSAVLSAFVLLRAV
       TGFSGDGKAIWDKKQYVSPVNPSQLFLYDTFPKNFFWGIGTGALQVEGSW
       KKDGKGPSIWDHFIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQ
       FSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPL
       ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
       GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
       GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
       VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
       NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
       EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
       QIIRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHL
       YVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA
       LDWASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLG
       LPEPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDI
       YNRSGNDTYGAAHNLLVAHALAWRLYDQQFRPSQRGAVSLSLHADWAEPA
       NPYADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSS
       SALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFL
       QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD
       RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK
       AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
       GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS

(xiii) huBeta_Klotho(1-81, 194-1044)(muBeta KLOTHO 82P-193L)
                                                         (SEQ ID NO: 467)
       MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAV
       TGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFSWGVGTGAFQVEGSW
       KTDGRGPSIWDRYVYSHLRGVNGTDRSTDSYIFLEKDLLALDFLGVSFYQ
       FSISWPRLFPNGTVAAVNAQGLRYYRALLDSLVLRNIEPIVTLYHWDLPL
       ALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGY
       GTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHNYNTHFRPHQKGWLSITL
       GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFS
       VLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREAL
       NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLD
       EIRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYK
       QIIRENGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHL
       YVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA
       LDWASVLPTGNLSAVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLG
       LPEPLLHADGWLNPSTAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDI
       YNRSGNDTYGAAHNLLVAHALAWRLYDQQFRPSQRGAVSLSLHADWAEPA
       NPYADSHWRAAERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSS
       SALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFL
       QDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDDQALEDD
       RLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFK
       AKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFL
       GCCFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS
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Various antigen binding proteins provided herein, as well as human FGF21, were tested for the ability to activate the chimeras in L6 cells. FIG. **30** correlates the observed results with each tested molecule.

These data indicate that while human FGF21 was able to activate FGFR1c combined with all of the human/mouse β-Klotho chimeras ("+" sign indicate activity on the receptor), the substitutions of mouse sequences into human β-Klotho affected the activities of 16H7, 37D3, and 39F7. See FIG. **30**. These results suggest that β-Klotho sequences 1-81, 302-522, and 849-1044 are important for the activities of agonistic antigen binding proteins and may represent an important epitope for their function.

Example 12

Protease Protection Analysis

Regions of the human FGF21 receptor bound by the antigen binding proteins that bind human FGF21 receptor, e.g., FGFR1c, β-Klotho or FGFR1c and β-Klotho complex can be identified by fragmenting human FGF21 receptor into peptides with specific proteases, e.g., AspN, Lys-C, chymotrypsin or trypsin. The sequence of the resulting human FGF21 receptor peptides (i.e., both disulfide- and non-disulfide-containing peptide fragments from FGFR1c and β-Klotho portions) can then be determined. In one example, soluble forms of a human FGF21 receptor, e.g., a complex comprising the FGFR1c ECD-Fc and β-Klotho ECD-Fc heterodimer described herein can be digested with AspN (which cleaves after aspartic acid and some glutamic acid residues at the amino end) by incubating about 100 μg of soluble FGF21 receptor at 1.0 mg/ml in 0.1M sodium phosphate (pH 6.5) for 20 hrs at 37° C. with 2 μg of AspN.

A peptide profile of the AspN digests can then be generated on HPLC chromatography while a control digestion with a similar amount of antibody is expected to be essentially resistant to AspN endoprotease. A protease protection assay can then be performed to determine the proteolytic digestion of human FGF21 receptor in the presence of the antigen binding proteins. The general principle of this assay is that binding of an antigen binding protein to the FGF21 receptor can result in protection of certain specific protease cleavage sites and this information can be used to determine the region or portion of FGF21 receptor where the antigen binding protein binds.

Briefly, the peptide digests can be subjected to HPLC peptide mapping; the individual peaks are collected, and the peptides are identified and mapped by on-line electrospray ionization LC-MS (ESI-LC-MS) analyses and/or by N-terminal sequencing. HPLC analyses for these studies can be performed using a narrow bore reverse-phase C18 column (Agilent Technologies) for off-line analysis and using a capillary reverse phase C18 column (The Separation Group) for LC-MS. HPLC peptide mapping can be performed with a linear gradient from 0.05% trifluoroacetic acid (mobile phase A) to 90% acetonitrile in 0.05% trifluoroacetic acid. Columns can be developed at desirable flow rate for narrow bore HPLC for off-line or on-line LC-MS analyses, and for capillary HPLC for on-line LC-MS analyses.

Sequence analyses can be conducted by on-line LC-MS/MS and by Edman sequencing on the peptide peaks recovered from HPLC. On-line ESI LC-MS analyses of the peptide digest can be performed to determine the precise mass and sequence of the peptides that are separated by HPLC. The identities of selected peptides present in the peptide peaks from the protease digestion can thus be determined.

Example 13

Cynomolgous Monkey Study

A construct encoding the antigen binding protein designated herein as 16H7 was generated using the methodology disclosed in Examples 1-3. 16H7 was expressed, purified and characterized as described in Examples 1-5 and was studied in vivo in obese cynomolgus monkeys. 16H7 is a fully human IgG1 antibody and is described by the sequences provided in Tables 1-4, supra.

Example 13.1

Study Design

The study was conducted in obese cynomolgus monkeys. The monkeys were 8-19 years old. Their body weights ranged from 7-14 kg and BMI ranged from 36-74 kg/m^2. Monkeys were acclimated for 6 weeks prior to the initiation of compound administration. During the acclimation period, the monkeys were familiarized with study-related procedures, including chair-restraint, subcutaneous injection (PBS, 0.1 ml/kg), gavage (water, 10 ml/kg), and blood drawn for non-OGTT and OGTT samples. After 4 weeks of training, baseline OGTT and plasma metabolic parameters were measured. 20 monkeys were selected and randomized into two treatment groups to achieve similar baseline levels of body weight, glucose OGTT profiles, and plasma glucose and triglyceride levels.

The study was conducted in a blinded fashion. Vehicle (n=10), 16H7 (n=10). Compound was given every other week (5 mg/kg). On the week when animals were not injected with 16H7, they received vehicle injection instead. After 2 injections of 16H7, animals were monitored during an additional 6 weeks for compound washout and recovery from treatments. Food intake, body weight, clinical chemistry and OGTT were monitored throughout the study. Food intake was measured every meal. Body weight was measured weekly. Blood samples were collected on different days in fasted or fed state to measure glucose, insulin and triglyceride levels. OGTTs were conducted every two weeks after the initiation of the study. The day starting the treatment is designated as 0 and the detailed study plan is shown in FIG. **14**.

The results presented in this Example represent data collected throughout the 68 days of the study.

Example 13.2

Effect of 16H7 on Food Intake

Animals were fed twice a day, with each animal receiving 120 g of formulated food established during the acclimation period. The remaining food was removed and weighed after each meal to calculate food intake. The feeding times were from 8:00 AM to 8:30 AM (±30 minutes) and then from 4:30 PM to 5:00 PM (±30 minutes). Fruit (150 g) was supplied to each animal at 11:30 to 12:30 PM (±30 minutes) every day.

Compared with vehicle, 16H7 reduced food intake in the monkeys. The effect diminished and the food intake returned to close to baseline or control levels after about 21 days of treatment. 16H7 did not have a significant effect on AM food intake (FIG. **15**) and only modestly reduced food intake on PM meal during the treatment (FIG. **16**). An increase in AM food intake was seen after day 49 (FIG. **15**). Throughout the study (and even during the acclimation period), fruit intake seemed lower in the 16H7 group compared to the vehicle group. Overall, 16H7 showed a significant effect on inhibiting food intake.

Example 13.3

Effect of 16H7 on Body Weight

Body weight was monitored weekly throughout the study. Over the course of the 4 week treatments, the body weight of animals treated with vehicle remained constant while body weight of animals treated with 16H7 progressively decreased. Body weight did not return to baseline by the end of the 6 weeks wash out period (FIG. **17**).

Example 13.4

Effect of 16H7 on Body Mass Index (BMI), Abdominal Circumference (AC) and Skin Fold Thickness (SFT)

BMI, AC and SFT were monitored weekly throughout the study, both pre- and post-administration of test compound when the body weight was taken. BMI is defined as the individual's body weight divided by the square of his or her height. SFT is the thickness of a double layer of skin and the fat beneath it as measured with a caliper. BMI, SFT and AC are relatively accurate, simple, and inexpensive measurements of body composition, particularly indicative of subcutaneous fat. Animals treated with vehicle showed relatively stable BMI, SFT and AC throughout the study. Animals treated with 16H7 showed decreased levels of BMI, AC and SFT over the course of the 4 week study, suggesting that 16H7 compound resulted in reduction of fat mass. Results are shown in FIGS. **18**-**20**, respectively. These measured parameters did not come back to baseline values at the end of the 6 weeks wash out period.

Example 13.5

Effect of 16H7 on Oral Glucose Tolerance Test (OGTT)

OGTTs were conducted before and after initiation of treatments. Before 16H7 injections baseline values for glucose and insulin levels were measured throughout the OGTT (FIGS. **21** and **22**, respectively) and were not statistically significantly different between the vehicle and 16H7 groups. Post-dose OGTTs were performed every two weeks during the treatment period and after 3 weeks of wash out period. 16H7 slightly improved glucose tolerance after 4 weeks of treatment and 3 weeks of wash out period. The animal model used is not glucose intolerant explaining the modest effects observed (FIG. **21**). Insulin levels were statistically significantly decreased in animals treated with 16H7 (significance observed at time 0 during the OGTT performed after 2 weeks of treatment, at time 0 and 15 minutes during the OGTT performed after 4 weeks of treatment and at time 0 and 60 minutes during the OGTT performed after 2 weeks of treatment) (FIG. **22**).

Example 13.6

Effect of 16H7 on Fasting and Fed Blood Glucose and Insulin Levels

Blood was collected from overnight fasted animals or in fed conditions after the AM feeding. In the fasted conditions, blood drawn was conducted weekly 5 days post each injection. In the fed conditions, blood drawn was conducted on days 2, 11, 16, 25 and 46 post first injection. 16H7 did not reduce fasting or fed blood glucose levels (FIGS. **23** and **25**). No hypoglycemia was observed in any of the monkeys treated with 16H7. 16H7 did, however, result in a statistically significant decrease in fasting and fed plasma insulin levels (FIGS. **24** and **26**).

Example 13.7

Effect of 16H7 on Triglyceride Levels

Measurements were made from the same samples collected for glucose and insulin measurements. Triglyceride levels were significantly reduced in animals treated with 16H7 when measured in fasted or fed conditions (FIGS. **27** and **28**).

Example 13.8

Conclusions

In a study conducted in male obese cynomolgus monkeys, animals treated with 16H7 showed improved metabolic parameters. Body weight was reduced and body composition was improved. Short-term reduction of food intake was observed and the effect diminished and the food intake recovered to baseline or control levels at 21 days into the study. Fasting insulin and triglyceride levels were also reduced by 16H7. Insulin levels measured during OGTT were also improved.

Example 14

Variant Forms of Antigen Binding Proteins 16H7 and 22H5

Antigen binding proteins 16H7 and 22H5, which are described herein in Tables 1-4, were mutated to impart different properties to the molecule, such as changes in solubility, pI, overall charge, immunogenicity in humans and in animal models, stability, etc. The mutations comprised additions, deletions or substitutions in either the light chain (designated "LC", SEQ ID NO:14) or heavy chain (designated "HC", SEQ ID NO:32) of the molecule. The disclosed single point mutations were made individually or two or more mutations were combined.

Examples of mutations and combinations of mutations that were introduced into the 16H7 heavy and light chain sequences include the following:

I83K (in 16H7 heavy chain) (SEQ ID NO:396)

E16Q (in 16H7 heavy chain)+V24F (in 16H7 heavy chain)+I83T (in 16H7 heavy chain)+S100 I (in 16H7 heavy chain)+T119L (in 16H7 heavy chain) (SEQ ID NO:395)

D109S (in 16H7 heavy chain) (SEQ ID NO:401)

Deletion of Y107 (in 16H7 heavy chain) (SEQ ID NO:400)

Insertion of a Y residue on the N-terminal side of Y107 (in 16H7 heavy chain) (SEQ ID NO:405)

D88R+P89A+V90E (in 16H7 heavy chain) (SEQ ID NO:398)

D49Y (in 16H7 light chain) (SEQ ID NO:386)

D49A (in 16H7 light chain) (SEQ ID NO:387)

D91A (in 16H7 light chain) (SEQ ID NO:388)

D49A (in 16H7 light chain)+D91A (in 16H7 light chain) (SEQ ID NO:389)

Q16K (in 16H7 light chain) (SEQ ID NO:385)

Examples of mutations and combinations of mutations that were introduced into the 22H5 heavy and light chain sequences include the following:

N92Q (in 22H5 light chain) (SEQ ID NO:402)

S94A (in 22H5 light chain) (SEQ ID NO:403)

C109S (in 22H5 heavy chain) (SEQ ID NO:404)

Summarily, the generated antigen binding proteins comprised the following pairs of 16H7 heavy and light chains:

(i) 16H7 light chain (SEQ ID NO:14) paired with a 16H7 heavy chain comprising I83K (SEQ ID NO:396);

(ii) 16H7 light chain (SEQ ID NO:14) paired with a 16H7 heavy chain comprising E16Q, V24F, I83T, S100I, T119L (SEQ ID NO:395);

(iii) 16H7 light chain (SEQ ID NO:14) paired with a 16H7 heavy chain comprising D109S (SEQ ID NO:401);

(iv) 16H7 light chain (SEQ ID NO:14) paired with a 16H7 heavy chain comprising the deletion of Y107 (SEQ ID NO:400);

(v) 16H7 light chain (SEQ ID NO:14) paired with a 16H7 heavy chain comprising the insertion of a Y residue on the N-terminal side of Y107 (SEQ ID NO:405);

(vi) 16H7 light chain (SEQ ID NO:14) paired with a 16H7 heavy chain comprising D88R, P89A, V90E, (SEQ ID NO:398);

(vii) 16H7 heavy chain (SEQ ID NO:32) paired with a 16H7 light chain comprising D49Y (SEQ ID NO:386);

(viii) 16H7 heavy chain (SEQ ID NO:32) paired with a 16H7 light chain comprising D49A (LC) (SEQ ID NO:387);

(xi) 16H7 heavy chain (SEQ ID NO:32) paired with a 16H7 light chain comprising D91A (SEQ ID NO:388);

(ix) 16H7 heavy chain (SEQ ID NO:32) paired with a 16H7 light chain comprising D49A, D91A (SEQ ID NO:389);

(x) 16H7 heavy chain (SEQ ID NO:32) paired with a 16H7 light chain comprising Q16K (LC) (SEQ ID NO:385);

and the following pairs of 22H5 heavy and light chain sequences:

(xi) 22H5 heavy chain (SEQ ID NO:31) paired with a 22H5 light chain comprising N92Q (LC) (SEQ ID NO:402);

(xii) 22H5 heavy chain (SEQ ID NO:31) paired with a 22H5 light chain comprising S94A (LC) (SEQ ID NO:403);

(xiii) 22H5 light chain (SEQ ID NO:13) paired with a 22H5 heavy chain comprising C109S(HC) (SEQ ID NO:404);

(xiv) 22H5 light chain (SEQ ID NO:13) paired with a 22H5 heavy chain comprising an insertion of a tyrosine residue at position 107 (SEQ ID NO:405).

The amino acid sequences for the generated light chain variants are shown in Table 6:

TABLE 6A

Amino Acid Sequences of 16H7 and 22H5 Variants					
Core Sequence	Variation	Paired With	SEQ ID NO of Paired Sequence	Amino Acid Sequence of Variant Chain	SEQ ID NO:
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPG**K**TARITCGGNNIGSESVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGNNIGSESVHWYQQKPGQAPVLVVY**Y**DSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	386
16H7 light chain	D49A	H3	32	SYVLTQPPSVSVAPGQTARITCGGNNIGSESVHWYQQKPGQAPVLVVY**A**DSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	387
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPG**K**TARITCGGNNIGSESVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGNNIGSESVHWYQQKPGQAPVLVVY**Y**DSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	386
16H7 light chain	D91A	H3	32	SYVLTQPPSVSVAPGQTARITCGGNNIGSESVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVW**A**GNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	388
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPG**K**TARITCGGNNIGSESVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	385

TABLE 6A-continued

Amino Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Paired With	SEQ ID NO of Paired Sequence	Amino Acid Sequence of Variant Chain	SEQ ID NO:
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**Y** DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 light chain	D49A + D91A	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**A** DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVW**A**GNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	389
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPG**K**TARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**Y** DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	V24F	L3	14	QVTLKESGPVLVKPTETLTLTCT**F**S GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLIMTNMDPVDTATYYCAR SVVTGGYYYDGMDVWGQGTTVT VSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVP SSNFGTQTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVS HEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	390
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPG**K**TARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**Y** DSDRPSGIPERFSGSNSGNTATLTIS	386

TABLE 6A-continued

Core Sequence	Variation	Paired With	SEQ ID NO of Paired Sequence	Amino Acid Sequence of Variant Chain	SEQ ID NO:
				RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	
16H7 heavy chain	I83T	L3	14	QVTLKESGPVLVKPTETLTLTCTVS GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLTMTNMDPVDTATYYCA RSVVTGGYYYDGMDVWGQGTTVT VSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVP SSNFGTQTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVS HEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	391
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPGKTARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVYY DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	V24F + I83T	L3	14	QVTLKESGPVLVKPTETLTLTCTFS GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLTMTNMDPVDTATYYCA RSVVTGGYYYDGMDVWGQGTTVT VSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVP SSNFGTQTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVS HEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	392
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPGKTARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV	385

TABLE 6A-continued

Amino Acid Sequences of 16H7 and 22H5 Variants					
Core Sequence	Variation	Paired With	SEQ ID NO of Paired Sequence	Amino Acid Sequence of Variant Chain	SEQ ID NO:
				AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**Y** DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	E16Q + V24F + I83T	L3	14	QVTLKESGPVLVKPT**Q**TLTLTCT**F**S GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVL**T**MTNMDPVDTATYYCA RSVVTGGYYYDGMDVWGQGTTVT VSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVP SSNFGTQTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVS HEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	393
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPG**K**TARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**Y** DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	E16Q + V24F + I83T + T119L	L3	14	QVTLKESGPVLVKPT**Q**TLTLTCT**F**S GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVL**T**MTNMDPVDTATYYCA RSVVTGGYYYDGMDVWGQGT**L**V TVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTV PSSNFGTQTYTCNVDHKPSNTKVD KTVERKCCVECPPCPAPPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTFRVVSVLTVVHQDW LNGKEYKCKVSNKGLPAPIEKTISK TKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	394

TABLE 6A-continued

Amino Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Paired With	SEQ ID NO of Paired Sequence	Amino Acid Sequence of Variant Chain	SEQ ID NO:
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPGKTARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVYY DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	E16Q + V24F + I83T + S100I + T119L	L3	14	QVTLKESGPVLVKPTQTLTLTCTFS GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLTMTNMDPVDTATYYCA RIVVTGGYYYDGMDVWGQGTLVT VSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVP SSNFGTQTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVS HEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	395
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPGKTARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVYY DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	I83K	L3	14	QVTLKESGPVLVKPTETLTLTCTVS GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLKMTNMDPVDTATYYCA RSVVTGGYYYDGMDVWGQGTTVT VSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVP SSNFGTQTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVS HEDPEVQFNWYVDGVEVHNAKTK	396

TABLE 6A-continued

Amino Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Paired With	SEQ ID NO of Paired Sequence	Amino Acid Sequence of Variant Chain	SEQ ID NO:
				PREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPG**K**TARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**Y** DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	S100I	L3	14	QVTLKESGPVLVKPTETLTLTCTVS GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLIMTNMDPVDTATYYCAR **I**VVTGGYYYDGMDVWGQGTTVTV SSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPS SNFGTQTYTCNVDHKPSNTKVDKT VERKCCVECPPCPAPPVAGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSH EDPEVQFNWYVDGVEVHNAKTKP REEQFNSTFRVVSVLTVVHQDWLN GKEYKCKVSNKGLPAPIEKTISKTK GQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPEN NYKTTPPMLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK	397
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPG**K**TARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**Y** DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	D88R + P89A + V90E	L3	14	QVTLKESGPVLVKPTETLTLTCTVS GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLIMTNM**RAE**DTATYYCAR SVVTGGYYYDGMDVWGQGTTVT	398

TABLE 6A-continued

Amino Acid Sequences of 16H7 and 22H5 Variants					
Core Sequence	Variation	Paired With	SEQ ID NO of Paired Sequence	Amino Acid Sequence of Variant Chain	SEQ ID NO:
				VSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVP SSNFGTQTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVS HEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPGKTARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**Y** DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	D88R + P89A + V90E + S100I	L3	14	QVTLKESGPVLVKPTETLTLTCTVS GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLIMTNM**RAE**DTATYYCAR **I**VVTGGYYYDGMDVWGQGTTVTV SSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPS SNFGTQTYTCNVDHKPSNTKVDKT VERKCCVECPPCPAPPVAGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSH EDPEVQFNWYVDGVEVHNAKTKP REEQFNSTFRVVSVLTVVHQDWLN GKEYKCKVSNKGLPAPIEKTISKTK GQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPEN NYKTTPPMLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK	399
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPGKTARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**Y** DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV	386

TABLE 6A-continued

Amino Acid Sequences of 16H7 and 22H5 Variants					
Core Sequence	Variation	Paired With	SEQ ID NO of Paired Sequence	Amino Acid Sequence of Variant Chain	SEQ ID NO:
				AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	
16H7 heavy chain	Deletion of Y107	L3	14	QVTLKESGPVLVKPTETLTLTCTVS GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLIMTNMDPVDTATYYCAR SVVTGGYYDGMDVWGQGTTVTVS SASTKGPSVFPLAPCSRSTSESTAAL GCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSS NFGTQTYTCNVDHKPSNTKVDKTV ERKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHE DPEVQFNWYVDGVEVHNAKTKPR EEQFNSTFRVVSVLTVVHQDWLNG KEYKCKVSNKGLPAPIEKTISKTKG QPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENN YKTTPPMLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	400
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPGKTARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVYY DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	D109S	L3	14	QVTLKESGPVLVKPTETLTLTCTVS GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLIMTNMDPVDTATYYCAR SVVTGGYYYSGMDVWGQGTTVTV SSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPS SNFGTQTYTCNVDHKPSNTKVDKT VERKCCVECPPCPAPPVAGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSH EDPEVQFNWYVDGVEVHNAKTKP REEQFNSTFRVVSVLTVVHQDWLN GKEYKCKVSNKGLPAPIEKTISKTK GQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPEN NYKTTPPMLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK	401
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPGKTARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385

TABLE 6A-continued

Amino Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Paired With	SEQ ID NO of Paired Sequence	Amino Acid Sequence of Variant Chain	SEQ ID NO:
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGNNIGSESVHWYQQKPGQAPVLVVYYDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	386
22H5 light chain	N92Q	H2	31	SYVLTQPPSVSVAPGQTARITCGGNNIGSQSVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDQTSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	402
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPGKTARITCGGNNIGSESVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGNNIGSESVHWYQQKPGQAPVLVVYYDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	386
22H5 light chain	S94A	H2	31	SYVLTQPPSVSVAPGQTARITCGGNNIGSQSVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDNTADHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	403
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPGKTARITCGGNNIGSESVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGNNIGSESVHWYQQKPGQAPVLVVYYDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDGNSDHVVFGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	386

TABLE 6A-continued

Amino Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Paired With	SEQ ID NO of Paired Sequence	Amino Acid Sequence of Variant Chain	SEQ ID NO:
22H5 heavy chain	C109S	L2	13	QVTLKESGPVLVKPTETLTLTCTVS GFSLSNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLTMTNMDPVDTATYYCA RILLVGAYYY**S**GMDVWGQGTTVT VSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVP SSNFGTQTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVS HEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	404
16H7 light chain	Q16K	H3	32	SYVLTQPPSVSVAPG**K**TARITCGGN NIGSESVHWYQQKPGQAPVLVVYD DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	385
16H7 light chain	D49Y	H3	32	SYVLTQPPSVSVAPGQTARITCGGN NIGSESVHWYQQKPGQAPVLVVY**Y** DSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDGNSDHVV FGGGTKLTVLGQPKANPTVTLFPPS SEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS	386
16H7 heavy chain	Insertion of Y107	L3	14	QVTLKESGPVLVKPTETLTLTCTVS GFSLNNARMGVSWIRQPPGKALEW LAHIFSNDEKSYSTSLKSRLTISKDT SKSQVVLIMTNMDPVDTATYYCAR SVVTGGYYYYDGMDVWGQGTTV TVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTV PSSNFGTQTYTCNVDHKPSNTKVD KTVERKCCVECPPCPAPPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTFRVVSVLTVVHQDW LNGKEYKCKVSNKGLPAPIEKTISK TKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	405

TABLE 6B

Nucleic Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Nucleic Acid Sequence	SEQ ID NO:
16H7 light chain	Q16K	TCCTATGTGCTGACTCAGCCACCCTCGGTGT CAGTGGCCCCAGGA**AAG**ACGGCCAGGATT ACCTGTGGGGGAAACAACATTGGAAGTGA AAGTGTGCACTGGTACCAGCAGAAGCCAGG CCAGGCCCCTGTGCTGGTCGTCTATGATGA TAGCGACCGGCCCTCAGGGATCCCTGAGCG ATTCTCTGGCTCCAACTCTGGGAACACGGC CACCCTGACCATCAGCAGGGTCGAAGCCGG GGATGAGGCCGACTATTACTGTCAGGTGTG GGATGGTAATAGTGACCATGTGGTATTCGG CGGAGGGACCAAGCTGACCGTCCTAGGTCA GCCCAAGGCCAACCCCACTGTCACTCTGTT CCCGCCCTCCTCTGAGGAGCTCCAAGCCAA CAAGGCCACACTAGTGTGTCTGATCAGTGA CTTCTACCCGGGAGCTGTGACAGTGGCCTG GAAGGCAGATGGCAGCCCCGTCAAGGCGG GAGTGGAGACCACCAAACCCTCCAAACAG AGCAACAACAAGTACGCGGCCAGCAGCTA CCTGAGCCTGACGCCCGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCA TGAAGGGAGCACCGTGGAGAAGACAGTGG CCCCTACAGAATGTTCA	406
16H7 light chain	D49Y	TCCTATGTGCTGACTCAGCCACCCTCGGTGT CAGTGGCCCCAGGACAGACGGCCAGGATTA CCTGTGGGGGAAACAACATTGGAAGTGAA AGTGTGCACTGGTACCAGCAGAAGCCAGGC CAGGCCCCTGTGCTGGTCGTCTAT**TAT**GAT AGCGACCGGCCCTCAGGGATCCCTGAGCGA TTCTCTGGCTCCAACTCTGGGAACACGGCC ACCCTGACCATCAGCAGGGTCGAAGCCGGG GATGAGGCCGACTATTACTGTCAGGTGTGG GATGGTAATAGTGACCATGTGGTATTCGGC GGAGGGACCAAGCTGACCGTCCTAGGTCAG CCCAAGGCCAACCCCACTGTCACTCTGTTC CCGCCCTCCTCTGAGGAGCTCCAAGCCAAC AAGGCCACACTAGTGTGTCTGATCAGTGAC TTCTACCCGGGAGCTGTGACAGTGGCCTGG AAGGCAGATGGCAGCCCCGTCAAGGCGGG AGTGGAGACCACCAAACCCTCCAAACAGA GCAACAACAAGTACGCGGCCAGCAGCTACC TGAGCCTGACGCCCGAGCAGTGGAAGTCCC ACAGAAGCTACAGCTGCCAGGTCACGCATG AAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	407
16H7 light chain	D49A	TCCTATGTGCTGACTCAGCCACCCTCGGTGT CAGTGGCCCCAGGACAGACGGCCAGGATTA CCTGTGGGGGAAACAACATTGGAAGTGAA AGTGTGCACTGGTACCAGCAGAAGCCAGGC CAGGCCCCTGTGCTGGTCGTCTAT**GCT**GAT AGCGACCGGCCCTCAGGGATCCCTGAGCGA TTCTCTGGCTCCAACTCTGGGAACACGGCC ACCCTGACCATCAGCAGGGTCGAAGCCGGG GATGAGGCCGACTATTACTGTCAGGTGTGG GATGGTAATAGTGACCATGTGGTATTCGGC GGAGGGACCAAGCTGACCGTCCTAGGTCAG CCCAAGGCCAACCCCACTGTCACTCTGTTC CCGCCCTCCTCTGAGGAGCTCCAAGCCAAC AAGGCCACACTAGTGTGTCTGATCAGTGAC TTCTACCCGGGAGCTGTGACAGTGGCCTGG AAGGCAGATGGCAGCCCCGTCAAGGCGGG AGTGGAGACCACCAAACCCTCCAAACAGA GCAACAACAAGTACGCGGCCAGCAGCTACC TGAGCCTGACGCCCGAGCAGTGGAAGTCCC ACAGAAGCTACAGCTGCCAGGTCACGCATG AAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	408
16H7 light chain	D91A	TCCTATGTGCTGACTCAGCCACCCTCGGTGT CAGTGGCCCCAGGACAGACGGCCAGGATTA CCTGTGGGGGAAACAACATTGGAAGTGAA AGTGTGCACTGGTACCAGCAGAAGCCAGGC CAGGCCCCTGTGCTGGTCGTCTATGATGAT AGCGACCGGCCCTCAGGGATCCCTGAGCGA	409

TABLE 6B-continued

Nucleic Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Nucleic Acid Sequence	SEQ ID NO:
		TTCTCTGGCTCCAACTCTGGGAACACGGCC ACCCTGACCATCAGCAGGGTCGAAGCCGGG GATGAGGCCGACTATTACTGTCAGGTGTGG **GCT**GGTAATAGTGACCATGTGGTATTCGGC GGAGGGACCAAGCTGACCGTCCTAGGTCAG CCCAAGGCCAACCCCACTGTCACTCTGTTC CCGCCCTCCTCTGAGGAGCTCCAAGCCAAC AAGGCCACACTAGTGTGTCTGATCAGTGAC TTCTACCCGGGAGCTGTGACAGTGGCCTGG AAGGCAGATGGCAGCCCCGTCAAGGCGGG AGTGGAGACCACCAAACCCTCCAAACAGA GCAACAACAAGTACGCGGCCAGCAGCTACC TGAGCCTGACGCCCGAGCAGTGGAAGTCCC ACAGAAGCTACAGCTGCCAGGTCACGCATG AAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
16H7 light chain	D49A + D91A	TCCTATGTGCTGACTCAGCCACCCTCGGTGT CAGTGGCCCCAGGACAGACGGCCAGGATTA CCTGTGGGGGAAACAACATTGGAAGTGAA AGTGTGCACTGGTACCAGCAGAAGCCAGGC CAGGCCCCTGTGCTGGTCGTCTAT**GCT**GAT AGCGACCGGCCCTCAGGGATCCCTGAGCGA TTCTCTGGCTCCAACTCTGGGAACACGGCC ACCCTGACCATCAGCAGGGTCGAAGCCGGG GATGAGGCCGACTATTACTGTCAGGTGTGG **GCT**GGTAATAGTGACCATGTGGTATTCGGC GGAGGGACCAAGCTGACCGTCCTAGGTCAG CCCAAGGCCAACCCCACTGTCACTCTGTTC CCGCCCTCCTCTGAGGAGCTCCAAGCCAAC AAGGCCACACTAGTGTGTCTGATCAGTGAC TTCTACCCGGGAGCTGTGACAGTGGCCTGG AAGGCAGATGGCAGCCCCGTCAAGGCGGG AGTGGAGACCACCAAACCCTCCAAACAGA GCAACAACAAGTACGCGGCCAGCAGCTACC TGAGCCTGACGCCCGAGCAGTGGAAGTCCC ACAGAAGCTACAGCTGCCAGGTCACGCATG AAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	410
16H7 heavy chain	V24F	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACAGAGACCCTCACGCTG ACCTGCACCTTCTCTGGGTTCTCACTCAACA ATGCTAGAATGGGTGTGAGCTGGATCCGTC AGCCCCCAGGGAAGGCCCTGGAGTGGCTTG CACACATTTTTCGAATGACGAAAAATCCT ACAGCACATCTCTGAAGAGCAGGCTCACCA TCTCCAAGGACACCTCCAAAAGCCAGGTGG TCCTAATTATGACCAACATGGACCCTGTGG ACACAGCCACATATTACTGTGCACGGTCAG TAGTAACTGGCGGCTACTACTACGACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCA CCGTCTCTAGTGCCTCCACCAAGGGCCCAT CGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTG AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC AAAACCAAAGGGCAGCCCCGAGAACCACA	411

TABLE 6B-continued

Nucleic Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Nucleic Acid Sequence	SEQ ID NO:
		GGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AA	
16H7 heavy chain	I83T	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACAGAGACCCTCACGCTG ACCTGCACCGTGTCTGGGTTCTCACTCAAC AATGCTAGAATGGGTGTGAGCTGGATCCGT CAGCCCCCAGGGAAGGCCCTGGAGTGGCTT GCACACATTTTTTCGAATGACGAAAAATCC TACAGCACATCTCTGAAGAGCAGGCTCACC ATCTCCAAGGACACCTCCAAAAGCCAGGTG GTCCTAACCATGACCAACATGGACCCTGTG GACACAGCCACATATTACTGTGCACGGTCA GTAGTAACTGGCGGCTACTACTACGACGGT ATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCTAGTGCCTCCACCAAGGGCCCA TCGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTG AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC AAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AA	412
16H7 heavy chain	V24F + I83T	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACAGAGACCCTCACGCTG ACCTGCACCTTCTCTGGGTTCTCACTCAACA ATGCTAGAATGGGTGTGAGCTGGATCCGTC AGCCCCCAGGGAAGGCCCTGGAGTGGCTTG CACACATTTTTTCGAATGACGAAAAATCCT ACAGCACATCTCTGAAGAGCAGGCTCACCA TCTCCAAGGACACCTCCAAAAGCCAGGTGG TCCTAACCATGACCAACATGGACCCTGTGG ACACAGCCACATATTACTGTGCACGGTCAG TAGTAACTGGCGGCTACTACTACGACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCA CCGTCTCTAGTGCCTCCACCAAGGGCCCAT CGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG	413

TABLE 6B-continued

Nucleic Acid Sequences of 16H7 and 22H5 Variants			
Core Sequence	Variation	Nucleic Acid Sequence	SEQ ID NO:
		TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTG AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC AAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AA	
16H7 heavy chain	E16Q + V24F + I83T	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACACAGACCCTCACGCTG ACCTGCACCTTCTCTGGGTTCTCACTCAACA ATGCTAGAATGGGTGTGAGCTGGATCCGTC AGCCCCCAGGGAAGGCCCTGGAGTGGCTTG CACACATTTTTTCGAATGACGAAAAATCCT ACAGCACATCTCTGAAGAGCAGGCTCACCA TCTCCAAGGACACCTCCAAAAGCCAGGTGG TCCTAACCATGACCAACATGGACCCTGTGG ACACAGCCACATATTACTGTGCACGGTCAG TAGTAACTGGCGGCTACTACTACGACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCA CCGTCTCTAGTGCCTCCACCAAGGGCCCAT CGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTG AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC AAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACA	414

TABLE 6B-continued

Nucleic Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Nucleic Acid Sequence	SEQ ID NO:
		CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AA	
16H7 heavy chain	E16Q + V24F + I83T + T119L	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACACAGACCCTCACGCTG ACCTGCACCTTCTCTGGGTTCTCACTCAACA ATGCTAGAATGGGTGTGAGCTGGATCCGTC AGCCCCCAGGGAAGGCCCTGGAGTGGCTTG CACACATTTTTTCGAATGACGAAAAATCCT ACAGCACATCTCTGAAGAGCAGGCTCACCA TCTCCAAGGACACCTCCAAAAGCCAGGTGG TCCTAACCATGACCAACATGGACCCTGTGG ACACAGCCACATATTACTGTGCACGGTCAG TAGTAACTGGCGGCTACTACTACGACGGTA TGGACGTCTGGGGCCAAGGGACCCTGGTCA CCGTCTCTAGTGCCTCCACCAAGGGCCCAT CGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTG AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC AAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AA	415
16H7 heavy chain	E16Q + V24F + I83T + S100I + T119L	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACACAGACCCTCACGCTG ACCTGCACCTTCTCTGGGTTCTCACTCAACA ATGCTAGAATGGGTGTGAGCTGGATCCGTC AGCCCCCAGGGAAGGCCCTGGAGTGGCTTG CACACATTTTTTCGAATGACGAAAAATCCT ACAGCACATCTCTGAAGAGCAGGCTCACCA TCTCCAAGGACACCTCCAAAAGCCAGGTGG TCCTAACCATGACCAACATGGACCCTGTGG ACACAGCCACATATTACTGTGCACGGATCG TAGTAACTGGCGGCTACTACTACGACGGTA TGGACGTCTGGGGCCAAGGGACCCTGGTCA CCGTCTCTAGTGCCTCCACCAAGGGCCCAT CGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA	416

TABLE 6B-continued

Nucleic Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Nucleic Acid Sequence	SEQ ID NO:
		AGGACACCCTCATGATCTCCCGGACCCCTG AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC AAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AA	
16H7 heavy chain	I83K	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACAGAGACCCTCACGCTG ACCTGCACCGTGTCTGGGTTCTCACTCAAC AATGCTAGAATGGGTGTGAGCTGGATCCGT CAGCCCCCAGGGAAGGCCCTGGAGTGGCTT GCACACATTTTTTCGAATGACGAAAAATCC TACAGCACATCTCTGAAGAGCAGGCTCACC ATCTCCAAGGACACCTCCAAAAGCCAGGTG GTCCTAAAGATGACCAACATGGACCCTGTG GACACAGCCACATATTACTGTGCACGGTCA GTAGTAACTGGCGGCTACTACTACGACGGT ATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCTAGTGCCTCCACCAAGGGCCCA TCGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTG AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC AAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AA	417
16H7 heavy chain	S100I	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACAGAGACCCTCACGCTG ACCTGCACCGTGTCTGGGTTCTCACTCAAC AATGCTAGAATGGGTGTGAGCTGGATCCGT CAGCCCCCAGGGAAGGCCCTGGAGTGGCTT GCACACATTTTTTCGAATGACGAAAAATCC	418

TABLE 6B-continued

Nucleic Acid Sequences of 16H7 and 22H5 Variants			
Core Sequence	Variation	Nucleic Acid Sequence	SEQ ID NO:
		TACAGCACATCTCTGAAGAGCAGGCTCACC ATCTCCAAGGACACCTCCAAAAGCCAGGTG GTCCTAATTATGACCAACATGGACCCTGTG GACACAGCCACATATTACTGTGCACGGATC GTAGTAACTGGCGGCTACTACTACGACGGT ATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCTAGTGCCTCCACCAAGGGCCCA TCGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTG AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC AAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AA	
16H7 heavy chain	D88R + P89A + V90E	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACAGAGACCCTCACGCTG ACCTGCACCGTGTCTGGGTTCTCACTCAAC AATGCTAGAATGGGTGTGAGCTGGATCCGT CAGCCCCCAGGGAAGGCCCTGGAGTGGCTT GCACACATTTTTTCGAATGACGAAAAATCC TACAGCACATCTCTGAAGAGCAGGCTCACC ATCTCCAAGGACACCTCCAAAAGCCAGGTG GTCCTAATTATGACCAACATGAGAGCTGAG GACACAGCCACATATTACTGTGCACGGTCA GTAGTAACTGGCGGCTACTACTACGACGGT ATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCTAGTGCCTCCACCAAGGGCCCA TCGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTG AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC	419

TABLE 6B-continued

<table>
<tr><th colspan="4">Nucleic Acid Sequences of 16H7 and 22H5 Variants</th></tr>
<tr><th>Core Sequence</th><th>Variation</th><th>Nucleic Acid Sequence</th><th>SEQ ID NO:</th></tr>
<tr><td></td><td></td><td>AAAACCAAAGGGCAGCCCCGAGAACCACA
GGTGTACACCCTGCCCCCATCCCGGGAGGA
GATGACCAAGAACCAGGTCAGCCTGACCTG
CCTGGTCAAAGGCTTCTACCCCAGCGACAT
CGCCGTGGAGTGGGAGAGCAATGGGCAGC
CGGAGAACAACTACAAGACCACACCTCCCA
TGCTGGACTCCGACGGCTCCTTCTTCCTCTA
CAGCAAGCTCACCGTGGACAAGAGCAGGT
GGCAGCAGGGGAACGTCTTCTCATGCTCCG
TGATGCATGAGGCTCTGCACAACCACTACA
CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA
AA</td><td></td></tr>
<tr><td>16H7 heavy chain</td><td>D88R + P89A + V90E + S100I</td><td>CAGGTCACCTTGAAGGAGTCTGGTCCTGTG
CTGGTGAAACCCACAGAGACCCTCACGCTG
ACCTGCACCGTGTCTGGGTTCTCACTCAAC
AATGCTAGAATGGGTGTGAGCTGGATCCGT
CAGCCCCCAGGGAAGGCCCTGGAGTGGCTT
GCACACATTTTTTCGAATGACGAAAAATCC
TACAGCACATCTCTGAAGAGCAGGCTCACC
ATCTCCAAGGACACCTCCAAAAGCCAGGTG
GTCCTAATTATGACCAACATGAGAGCTGAG
GACACAGCCACATATTACTGTGCACGGATC
GTAGTAACTGGCGGCTACTACTACGACGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTC
ACCGTCTCTAGTGCCTCCACCAAGGGCCCA
TCGGTCTTCCCCCTGGCGCCCTGCTCCAGGA
GCACCTCCGAGAGCACAGCGGCCCTGGGCT
GCCTGGTCAAGGACTACTTCCCCGAACCGG
TGACGGTGTCGTGGAACTCAGGCGCTCTGA
CCAGCGGCGTGCACACCTTCCCAGCTGTCC
TACAGTCCTCAGGACTCTACTCCCTCAGCA
GCGTGGTGACCGTGCCCTCCAGCAACTTCG
GCACCCAGACCTACACCTGCAACGTAGATC
ACAAGCCCAGCAACACCAAGGTGGACAAG
ACAGTTGAGCGCAAATGTTGTGTCGAGTGC
CCACCGTGCCCAGCACCACCTGTGGCAGGA
CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA
AGGACACCCTCATGATCTCCCGGACCCCTG
AGGTCACGTGCGTGGTGGTGGACGTGAGCC
ACGAAGACCCCGAGGTCCAGTTCAACTGGT
ACGTGGACGGCGTGGAGGTGCATAATGCCA
AGACAAAGCCACGGGAGGAGCAGTTCAAC
AGCACGTTCCGTGTGGTCAGCGTCCTCACC
GTTGTGCACCAGGACTGGCTGAACGGCAAG
GAGTACAAGTGCAAGGTCTCCAACAAAGGC
CTCCCAGCCCCCATCGAGAAAACCATCTCC
AAAACCAAAGGGCAGCCCCGAGAACCACA
GGTGTACACCCTGCCCCCATCCCGGGAGGA
GATGACCAAGAACCAGGTCAGCCTGACCTG
CCTGGTCAAAGGCTTCTACCCCAGCGACAT
CGCCGTGGAGTGGGAGAGCAATGGGCAGC
CGGAGAACAACTACAAGACCACACCTCCCA
TGCTGGACTCCGACGGCTCCTTCTTCCTCTA
CAGCAAGCTCACCGTGGACAAGAGCAGGT
GGCAGCAGGGGAACGTCTTCTCATGCTCCG
TGATGCATGAGGCTCTGCACAACCACTACA
CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA
AA</td><td>420</td></tr>
<tr><td>16H7 heavy chain</td><td>Deletion of Y107</td><td>CAGGTCACCTTGAAGGAGTCTGGTCCTGTG
CTGGTGAAACCCACAGAGACCCTCACGCTG
ACCTGCACCGTGTCTGGGTTCTCACTCAAC
AATGCTAGAATGGGTGTGAGCTGGATCCGT
CAGCCCCCAGGGAAGGCCCTGGAGTGGCTT
GCACACATTTTTTCGAATGACGAAAAATCC
TACAGCACATCTCTGAAGAGCAGGCTCACC
ATCTCCAAGGACACCTCCAAAAGCCAGGTG
GTCCTAATTATGACCAACATGGACCCTGTG
GACACAGCCACATATTACTGTGCACGGTCA
GTAGTAACTGGCGGCTAC|TACGACGGTATG
GACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCTAGTGCCTCCACCAAGGGCCCATCG
GTCTTCCCCCTGGCGCCCTGCTCCAGGAGC
ACCTCCGAGAGCACAGCGGCCCTGGGCTGC</td><td>421</td></tr>
</table>

TABLE 6B-continued

Nucleic Acid Sequences of 16H7 and 22H5 Variants			
Core Sequence	Variation	Nucleic Acid Sequence	SEQ ID NO:
		CTGGTCAAGGACTACTTCCCCGAACCGGTG ACGGTGTCGTGGAACTCAGGCGCTCTGACC AGCGGCGTGCACACCTTCCCAGCTGTCCTA CAGTCCTCAGGACTCTACTCCCTCAGCAGC GTGGTGACCGTGCCCTCCAGCAACTTCGGC ACCCAGACCTACACCTGCAACGTAGATCAC AAGCCCAGCAACACCAAGGTGGACAAGAC AGTTGAGCGCAAATGTTGTGTCGAGTGCCC ACCGTGCCCAGCACCACCTGTGGCAGGACC GTCAGTCTTCCTCTTCCCCCCAAAACCCAAG GACACCCTCATGATCTCCCGGACCCCTGAG GTCACGTGCGTGGTGGTGGACGTGAGCCAC GAAGACCCCGAGGTCCAGTTCAACTGGTAC GTGGACGGCGTGGAGGTGCATAATGCCAAG ACAAAGCCACGGGAGGAGCAGTTCAACAG CACGTTCCGTGTGGTCAGCGTCCTCACCGTT GTGCACCAGGACTGGCTGAACGGCAAGGA GTACAAGTGCAAGGTCTCCAACAAAGGCCT CCCAGCCCCCATCGAGAAAACCATCTCCAA AACCAAAGGGCAGCCCCGAGAACCACAGG TGTACACCCTGCCCCCATCCCGGGAGGAGA TGACCAAGAACCAGGTCAGCCTGACCTGCC TGGTCAAAGGCTTCTACCCCAGCGACATCG CCGTGGAGTGGGAGAGCAATGGGCAGCCG GAGAACAACTACAAGACCACACCTCCCATG CTGGACTCCGACGGCTCCTTCTTCCTCTACA GCAAGCTCACCGTGGACAAGAGCAGGTGG CAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACG CAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
16H7 heavy chain	D109S	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACAGAGACCCTCACGCTG ACCTGCACCGTGTCTGGGTTCTCACTCAAC AATGCTAGAATGGGTGTGAGCTGGATCCGT CAGCCCCCAGGGAAGGCCCTGGAGTGGCTT GCACACATTTTTTCGAATGACGAAAAATCC TACAGCACATCTCTGAAGAGCAGGCTCACC ATCTCCAAGGACACCTCCAAAAGCCAGGTG GTCCTAATTATGACCAACATGGACCCTGTG GACACAGCCACATATTACTGTGCACGGTCA GTAGTAACTGGCGGCTACTACTACAGCGGT ATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCTAGTGCCTCCACCAAGGGCCCA TCGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTG AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC AAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACA	422

TABLE 6B-continued

Nucleic Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Nucleic Acid Sequence	SEQ ID NO:
		CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AA	
22H5 light chain	N92Q	TCCTATGTGCTGACTCAGCCACCCTCGGTGT CAGTGGCCCCAGGACAGACGGCCAGGATTA CCTGTGGGGGAAACAACATTGGAAGTCAAA GTGTGCACTGGTACCAGCAGAAGCCAGGCC AGGCCCCTGTCCTGGTCGTCTATGATGATA GCGACCGGCCCTCAGGGATCCCTGAGCGAT TCTCTGGTTCCAACTCTGGGAACACGGCCA CCCTGACCATCAGCAGGGTCGAAGCCGGGG ATGAGGCCGACTATTACTGTCAGGTGTGGG AT**CAG**ACTAGTGATCATGTGGTATTCGGCG GGGGGACCAAGCTGACCGTCCTAGGTCAGC CCAAGGCCAACCCCACTGTCACTCTGTTCC CGCCCTCCTCTGAGGAGCTCCAAGCCAACA AGGCCACACTAGTGTGTCTGATCAGTGACT TCTACCCGGGAGCTGTGACAGTGGCCTGGA AGGCAGATGGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCAAACCCTCCAAACAGAGC AACAACAAGTACGCGGCCAGCAGCTACCTG AGCCTGACGCCCGAGCAGTGGAAGTCCCAC AGAAGCTACAGCTGCCAGGTCACGCATGAA GGGAGCACCGTGGAGAAGACAGTGGCCCC TACAGAATGTTCA	423
22H5 light chain	S94A	TCCTATGTGCTGACTCAGCCACCCTCGGTGT CAGTGGCCCCAGGACAGACGGCCAGGATTA CCTGTGGGGGAAACAACATTGGAAGTCAAA GTGTGCACTGGTACCAGCAGAAGCCAGGCC AGGCCCCTGTCCTGGTCGTCTATGATGATA GCGACCGGCCCTCAGGGATCCCTGAGCGAT TCTCTGGTTCCAACTCTGGGAACACGGCCA CCCTGACCATCAGCAGGGTCGAAGCCGGGG ATGAGGCCGACTATTACTGTCAGGTGTGGG ATAATACT**GCT**GATCATGTGGTATTCGGCG GGGGGACCAAGCTGACCGTCCTAGGTCAGC CCAAGGCCAACCCCACTGTCACTCTGTTCC CGCCCTCCTCTGAGGAGCTCCAAGCCAACA AGGCCACACTAGTGTGTCTGATCAGTGACT TCTACCCGGGAGCTGTGACAGTGGCCTGGA AGGCAGATGGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCAAACCCTCCAAACAGAGC AACAACAAGTACGCGGCCAGCAGCTACCTG AGCCTGACGCCCGAGCAGTGGAAGTCCCAC AGAAGCTACAGCTGCCAGGTCACGCATGAA GGGAGCACCGTGGAGAAGACAGTGGCCCC TACAGAATGTTCA	424
22H5 heavy chain	C109S	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACAGAGACCCTCACGCTG ACCTGCACCGTGTCTGGGTTCTCACTCAGC AATGCTAGAATGGGTGTGAGCTGGATCCGT CAGCCCCCAGGGAAGGCCCTGGAGTGGCTT GCACACATTTTTTCGAATGACGAAAAATCC TACAGCACATCTCTGAAGAGCAGGCTCACC ATCTCCAAGGACACCTCCAAAAGCCAGGTG GTCCTTACCATGACCAACATGGACCCTGTG GACACAGCCACATATTACTGTGCACGGATA TTATTAGTGGGAGCTTACTACTAC**AGC**GGT ATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCTAGTGCCTCCACCAAGGGCCCA TCGGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGG TGACGGTGTCGTGGAACTCAGGCGCTCTGA CCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACCGTGCCCTCCAGCAACTTCG GCACCCAGACCTACACCTGCAACGTAGATC ACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTCGAGTGC CCACCGTGCCCAGCACCACCTGTGGCAGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTG	425

TABLE 6B-continued

Nucleic Acid Sequences of 16H7 and 22H5 Variants

Core Sequence	Variation	Nucleic Acid Sequence	SEQ ID NO:
		AGGTCACGTGCGTGGTGGTGGACGTGAGCC ACGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGC CTCCCAGCCCCCATCGAGAAAACCATCTCC AAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AA	
16H7 heavy chain	Insertion of Y107	CAGGTCACCTTGAAGGAGTCTGGTCCTGTG CTGGTGAAACCCACAGAGACCCTCACGCTG ACCTGCACCGTGTCTGGGTTCTCACTCAAC AATGCTAGAATGGGTGTGAGCTGGATCCGT CAGCCCCCAGGGAAGGCCCTGGAGTGGCTT GCACACATTTTTTCGAATGACGAAAAATCC TACAGCACATCTCTGAAGAGCAGGCTCACC ATCTCCAAGGACACCTCCAAAAGCCAGGTG GTCCTAATTATGACCAACATGGACCCTGTG GACACAGCCACATATTACTGTGCACGGTCA GTAGTAACTGGCGGCTAC**TAT**TACTACGAC GGTATGGACGTCTGGGGCCAAGGGACCACG GTCACCGTCTCTAGTGCCTCCACCAAGGGC CCATCGGTCTTCCCCCTGGCGCCCTGCTCCA GGAGCACCTCCGAGAGCACAGCGGCCCTGG GCTGCCTGGTCAAGGACTACTTCCCCGAAC CGGTGACGGTGTCGTGGAACTCAGGCGCTC TGACCAGCGGCGTGCACACCTTCCCAGCTG TCCTACAGTCCTCAGGACTCTACTCCCTCAG CAGCGTGGTGACCGTGCCCTCCAGCAACTT CGGCACCCAGACCTACACCTGCAACGTAGA TCACAAGCCCAGCAACACCAAGGTGGACA AGACAGTTGAGCGCAAATGTTGTGTCGAGT GCCCACCGTGCCCAGCACCACCTGTGGCAG GACCGTCAGTCTTCCTCTTCCCCCCAAAACC CAAGGACACCCTCATGATCTCCCGGACCCC TGAGGTCACGTGCGTGGTGGTGGACGTGAG CCACGAAGACCCCGAGGTCCAGTTCAACTG GTACGTGGACGGCGTGGAGGTGCATAATGC CAAGACAAAGCCACGGGAGGAGCAGTTCA ACAGCACGTTCCGTGTGGTCAGCGTCCTCA CCGTTGTGCACCAGGACTGGCTGAACGGCA AGGAGTACAAGTGCAAGGTCTCCAACAAA GGCCTCCCAGCCCCCATCGAGAAAACCATC TCCAAAACCAAAGGGCAGCCCCGAGAACC ACAGGTGTACACCCTGCCCCCATCCCGGGA GGAGATGACCAAGAACCAGGTCAGCCTGA CCTGCCTGGTCAAAGGCTTCTACCCCAGCG ACATCGCCGTGGAGTGGGAGAGCAATGGG CAGCCGGAGAACAACTACAAGACCACACCT CCCATGCTGGACTCCGACGGCTCCTTCTTCC TCTACAGCAAGCTCACCGTGGACAAGAGCA GGTGGCAGCAGGGGAACGTCTTCTCATGCT CCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGG GTAAA	426

TABLE 6C

CDR Amino Acid Sequences of Variants

Core Sequence	Variation	Location of Mutation	CDR1	CDR1 SEQ ID NO	CDR2	CDR2 SEQ ID NO	CDR3	CDR3 SEQ ID NO:
16H7 light chain	Q16K	FW	GGNNIGSESV	166	DDSDRPS	176	QVWDGNSDHVV	188
16H7 light chain	D49Y	CDR2	GGNNIGSESVH	166	**Y**DSDRPS	427	QVWDGNSDHVV	188
16H7 light chain	D49A	CDR2	GGNNIGSESVH	166	**A**DSDRPS	428	QVWDGNSDHVV	188
16H7 light chain	D91A	CDR3	GGNNIGSESVH	166	DDSDRPS	176	QVW**A**GNSDHVV	429
16H7 light chain	D49A + D91A	CDR2, CDR3	GGNNIGSESVH	166	**A**DSDRPS	427	QVW**A**GNSDHVV	430
16H7 heavy chain	V24F	FW	NARMGVS	122	HIFSNDEKSYSTSLKS	133	SVVTGGYYYDGMDV	148
16H7 heavy chain	I83T	FW	NARMGVS	122	HIFSNDEKSYSTSLKS	133	SVVTGGYYYDGMDV	148
16H7 heavy chain	V24F + I83T	FW	NARMGVS	122	HIFSNDEKSYSTSLKS	133	SVVTGGYYYDGMDV	148
16H7 heavy chain	E16Q + V24F + I83T	FW	NARMGVS	122	HIFSNDEKSYSTSLKS	133	SVVTGGYYYDGMDV	148
16H7 heavy chain	E16Q + V24F + I83T + T19L	FW	NARMGVS	122	HIFSNDEKSYSTSLKS	133	SVVTGGYYYDGMDV	148
16H7 heavy chain	E16Q + V24F + I83T + S100I + T119L	FW, CDR3	NARMGVS	122	HIFSNDEKSYSTSLKS	133	**I**VVTGGYYYDGMDV	431
16H7 heavy chain	I83K	FW	NARMGVS	122	HIFSNDEKSYSTSLKS	133	SVVTGGYYYDGMDV	148
16H7 heavy chain	S100I	CDR3	NARMGVS	122	HIFSNDEKSYSTSLKS	133	**I**VVTGGYYYDGMDV	432
16H7 heavy chain	D88R + P89A + V90E	FW	NARMGDV	122	HIFSNDEKSYSTSLKS	133	SVVTGGYYYDGMDV	148
16H7 heavy chain	D88R + P89A + V90E + S101I	FW, CDR3	NARMGVS	122	HIFSNDEKSYSTSLKS	133	**I**VVTGGYYYDGMDV	433
16H7 heavy chain	Deletion of Y107	CDR3	NARMGVS	122	HIFSNDEKSYSTSLKS	133	SVVTGGYYDGMDV	434
16H7 heavy chain	D109S	CDR3	NARMGVS	122	HIFSNDEKSYSTSLKS	133	SVVTGGYY**S**GMDV	435
22H5 light chain	N92Q	CDR3	GGNNIGSQSVH	167	DDSDRPS	176	QVWD**Q**TSDHVV	436
22H5 light chain	S94A	CDR3	GGNNIGSQSVH	167	DDSDRPS	176	QVWDNT**A**DHVV	437
22H5 heavy chain	C109S	CDR3	NARMGVS	122	HIFSNDEKSYSTSLKS	133	ILLVGAYYY**S**GMDV	438
16H7 heavy chain	Insertion of Y107	CDR3	NARMGVS	122	HIFSNDEKSYSTSLKS	133	SVVTGGYYYYDGMDV	439

TABLE 6D

CDR Nucleic Acid Sequences of Variants

Core Sequence	Variation	Location of Mutation	CDR1	CDR1 SEQ ID NO	CDR2	CDR2 SEQ ID NO	CDR3	CDR3 SEQ ID NO:
16H7 light chain	Q16K	FW	GGGGGAAACAACATTGGAAGTGAAAGTGTGCAC	239	GATGATAGCGACCGGCCCTC	249	CAGGTGTGGGATGGTAATAGTGATCATGTGGTA	260
16H7 light chain	D49Y	CDR2	GGGGGAAACAACATTGGAAGTGAAAGTGTGCAC	239	**TAT**GATAGCGACCGGCCCTCA	442	CAGGTGTGGGATGGTAATAGTGATCATGTGGTA	260
16H7 light chain	D49A	CDR2	GGGGGAAACAACATTGGAAGTGAAAGTGTGCAC	239	**GCT**GATAGCGACCGGCCCTCA	443	CAGGTGTGGGATGGTAATAGTGATCATGTGGTA	260
16H7 light chain	D91A	CDR3	GGGGGAAACAACATTGGAAGTGAAAGTGTGCAC	239	GATGATAGCGACCGGCCCTCA	249	CAGGTGTGG**GCT**GGTAATAGTGACCATGTGGTA	445
16H7 light chain	D49A + D91A	CDR2, CDR3	GGGGGAAACAACATTGGAAGTGAAAGTGTGCAC	239	**GCT**GATAGCGACCGGCCCTCA	444	CAGGTGTGG**GCT**GGTAATAGTGACCATGTGGTA	445
16H7 heavy chain	V24F	FW	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	TCAGTAGTAACTGGCGGCTACTACTACGACGGTATGGACGTC	221
16H7 heavy chain	I83T	FW	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	TCAGTAGTAACTGGCGGCTACTACTACGACGGTATGGACGTC	221
16H7 heavy chain	V24F + I83T	FW	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	TCAGTAGTAACTGGCGGCTACTACTACGACGGTATGGACGTC	221
16H7 heavy chain	E16Q + V24F + I83T	FW	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	TCAGTAGTAACTGGCGGCTACTACTACGACGGTATGGACGTC	221
16H7 heavy chain	E16Q + V24F + I83T + T19L	FW	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	TCAGTAGTAACTGGCGGCTACTACTACGACGGTATGGACGTC	221
16H7 heavy chain	E16Q + V24F + I83T + S100I + T119L	FW, CDR3	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	ATCGTAGTAACTGGCGGCTACTACTACGACGGTATGGACGTC	446
16H7 heavy chain	I83K	FW	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	TCAGTAGTAACTGGCGGCTACTACTACGACGGTATGGACGTC	221
16H7 heavy chain	S100I	CDR3	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	ATCGTAGTAACTGGCGGCTACTACTACGACGGTATGGACGTC	446
16H7 heavy chain	D88R + P89A + V90E	FW	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	TCAGTAGTAACTGGCGGCTACTACTACGACGGTATGGACGTC	221
16H7 heavy chain	D88R + P89A + V90E + S100I	FW, CDR3	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	ATCGTAGTAACTGGCGGCTACTACTACGACGGTATGGACGTC	446
16H7 heavy chain	Deletion of Y107	CDR3	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	TCAGTAGTAACTGGCGGCTACTACGACGGTATGGACGTC	447

TABLE 6D-continued

CDR Nucleic Acid Sequences of Variants

Core Sequence	Variation	Location of Mutation	CDR1	CDR1 SEQ ID NO	CDR2	CDR2 SEQ ID NO	CDR3	CDR3 SEQ ID NO:
16H7 heavy chain	D109S	CDR3	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	TCAGTAGTAACTGGCGGCTACTACTACAGCGGTATGGACGTC	448
22H5 light chain	N92Q	CDR3	GGGGGAAACAACATTGGAAGTCAAAGTGTGCAC	240	GATGATAGCGACCGGCCCTCA	249	CAGGTGTGGGAT**CAG**ACTAGTGATCATGTGGTA	449
22H5 light chain	S94A	CDR3	GGGGGAAACAACATTGGAAGTCAAAGTGTGCAC	240	GATGATAGCGACCGGCCCTCA	249	CAGGTGTGGGATAATACT**GCT**GATCATGTGGTA	450
22H5 heavy chain	C109S	CDR3	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	ATATTATTAGTGGGAGCTTACTACTAC**AGC**GGTATGGACGTC	451
16H7 heavy chain	Insertion of Y107	CDR3	AATGCTAGAATGGGTGTGAGC	196	CACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGC	206	TCAGTAGTAACTGGCGGCTAC**TAT**TACTACGACGGTATGGACGTC	452

Additionally, a "hemibody" was generated and studied. This structure comprised the 16H7 light chain (L3; SEQ ID NO:50), which was paired with an engineered form of the 16H7 heavy chain; the engineered heavy chain comprised the 16H7 heavy chain (SEQ ID NO:32) joined via a $(G_4S)_8$ linker (SEQ ID NO:440) to an IgG2 Fc sequence (SEQ ID NO:441), which paired with the Fc sequence of the 16H7 heavy chain. The component parts of the hemibody have the following sequences:

16H7 Heavy Chain

(SEQ ID NO: 32)

MDMRVPAQLLGLLLLWLRGARCQVTLKESGPVLVKPTETLTLTCTV
SGFSLNNARMGVSWIRQPPGKALEWLAHIFSNDEKSYSTSLKSRLT
ISKDTSKSQVVLIMTNMDPVDTATYYCARSVVTGGYYYDGMDVWGQ
GTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCN
VDHKPSNTKVDKTVERKSSVECPPCPAPPVAGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFN
STFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSP

Linker

(SEQ ID NO: 440)

GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS

IgG2 Fc

(SEQ ID NO: 441)

ERKSSVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQ
DWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

The full hemibody heavy chain had the amino acid sequence shown below:

(SEQ ID NO: 453)

MDMRVPAQLLGLLLLSLRGARCQVTLKESGPVLVKPTETLTLTCTV
SGFSLNNARMGVSWIRQPPGKALEWLAHIFSNDEKSYSTSLKSRLT

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ISKDTSKSQVVLIMTNMDPVDTATYYCARSVVTGGYYYDGMDVWGQ
GTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCN
VDHKPSNTKVDKTVERKSSVECPPCPAPPVAGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHANKTKPREEQFN
STFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS
GGGGSERKSSVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVL
TVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLP
PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPPP
MLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSLPGK

which is encoded by the follow sequence:

(SEQ ID NO: 454)

ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGT
GGCTGAGAGGTGCGCGCTGTCAGGTCACCTTGAAGGAGTCTGGTCC
TGTGCTGGTGAAACCCACAGAGACCCTCACGCTGACCTGCACCGTG
TCTGGGTTCTCACTCAACAATGCTAGAATGGGTGTGAGCTGGATCC
GTCAGCCCCCAGGGAAGGCCCTGGAGTGGCTTGCACACATTTTTTC
GAATGACGAAAAATCCTACAGCACATCTCTGAAGAGCAGGCTCACC

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ATCTCCAAGGACACCTCCAAAAGCCAGGTGGTCCTAATTATGACCA
ACATGGACCCTGTGGACACAGCCACATATTACTGTGCACGGTCAGT
AGTAACTGGCGGCTACTACTACGACGGTATGGACGTCTGGGGCCAA
GGGACCACGGTCACCGTCTCTAGTGCCAGCACCAAGGGCCCCTCCG
TGTTCCCTCTGGCCCCCTGCAGCAGAAGCACCAGCGAGAGCACAGC
CGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCCGTGACC
GTGTCTTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTTC
CAGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGT
CACCGTGCCCAGCAGCAACTTCGGCACCCAGACCTACACCTGTAAC
GTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTGGAGC
GGAAGTCCAGCGTGGAGTGCCCTCCTTGTCCTGCCCCTCCTGTGGC
CGGACCTAGCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTG
ATGATCAGCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGACGTGT
CCCACGAGGACCCCGAGGTGCAGTTCAATTGGTACGTGGACGGGGT
GGAGGTGCACAACGCCAAGACCAAGCCCCGGGAGGAACAGTTCAAC
AGCACCTTCCGGGTGGTGTCCGTCCTCACCGTGGTGCACCAGGACT
GGCTGAACGGCAAAGAGTACAAGTGCAAGGTCTCCAACAAGGGCCT
GCCTGCCCCCATCGAGAAAACCATCAGCAAGACCAAGGGCCAGCCT
CGGGAGCCTCAGGTGTACACCCTGCCCCCCAGCCGGGAGGAAATGA
CCAAGAACCAGGTGTCCCTGACCTGCCTCGTGAAGGGCTTCTACCC
CAGCGATATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAAC
AACTACAAGACCACCCCCCCCATGCTGGACAGCGACGGCAGCTTCT
TCCTGTACTCCAAACTGACCGTGGACAAGAGCCGGTGGCAGCAGGG
CAACGTGTTCAGCTGTAGCGTGATGCACGAGGCCCTGCACAACCAC
TACACCCAGAAGTCCCTGAGCCTGTCTCCTGGCGGAGGCGGAGGAT
CTGGCGGCGGAGGAAGTGGAGGGGGCGGATCTGGTGGTGGAGGCAG
CGGCGGAGGTGGAAGTGGCGGTGGAGGATCCGGTGGAGGCGGCTCA
GGTGGCGGCGGAAGCGAGAGAAAGTCCTCCGTGGAGTGTCCACCAT
GCCCTGCTCCACCAGTGGCTGGCCCTTCCGTCTTTCTCTTTCCACC
TAAACCTAAGGATACACTCATGATCTCCAGAACTCCAGAGGTCACA
TGTGTGGTCGTCGATGTCAGTCATGAGGATCCTGAAGTCCAGTTTA
ACTGGTATGTGGATGGCGTCGAAGTCCATAATGCTAAGACAAAACC
TCGCGAAGAACAGTTTAACTCCACCTTTAGAGTCGTGAGCGTGCTG
ACAGTCGTCCATCAGGATTGGCTCAATGGGAAAGAATACAAATGTA
AAGTCTCTAACAAAGGACTGCCCGCTCCTATCGAAAAGACCATCTC
CAAAACAAAGGGGCAGCCCAGAGAGCCCCAGGTCTACACACTCCCA
CCCTCCAGAGAAGAGATGACAAAAAATCAGGTGTCACTCACCTGTC
TGGTCAAGGGGTTTTACCCCTCCGACATTGCCGTGGAATGGGAATC
CAATGGGCAGCCTGAAAACAATTATAAGACTACACCTCCTATGCTC
GACTCTGATGGGAGTTTCTTTCTCTACTCTAAACTCACAGTGGATA
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AGTCTAGATGGCAGCAGGGGAATGTCTTTTCCTGCTCCGTCATGCA
TGAAGCTCTCCACAATCATTATACACAGAAGTCTTTGTCCCTGTCC
CCCGGCAAG
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Example 14.1

β-Klotho Binding ELISA for Engineered Antibodies

The engineered forms of 16H7 and 22H5 were tested for β-Klotho binding using an ELISA assay. Conditions for the ELISA were as follows.

Streptavidin coated Maxisorp plates were incubated with 2 μg/ml β-Klotho overnight at 4 degrees. Antibodies were added in 3-fold serial dilutions starting at 1 μM for 1 hour at room temp. HRP conjugated anti-human Fc was used as the detector antibody. Signal was developed with Lumiglo and read on Envision.

Results of the ELISA assay are shown in FIG. **32**A-**32**C and indicate that most variants of 16H7 bound to human β-Klotho except for a mutant carrying insertion of tyrosine at position 107.

Example 14.2

Engineered Variants of 16H7 and 22H5Bind to Native Receptor Structure, as Shown by FACS

A FACS binding assay was performed with several of the engineered forms of 16H7 and 22H5. The experiments were performed as follows.

CHO cells stably expressing FGF21 receptor were treated with parent antibody 16H7 and 22H5 and also with engineered variants of them (1 μg per 1×10^6 cells in 100 μl PBS/0.5% BSA). Cells were incubated with the antibodies at 4° C. followed by two washes with PBS/BSA. Cells were then treated with FITC-labeled secondary antibodies at 4° C. followed by two washes. The cells were resuspended in 1 ml PBS/BSA and antibody binding was analyzed using a FACS Calibur instrument.

Consistent with ELISA results, most of engineered variants of FGF21 receptor agonistic antibodies tested bind well to cell surface FGF21 receptor in FACS. This observation further confirmed that the guided engineering of FGF21 receptor agonistic antibodies maintain binding to the native structure. In one mutant, in which CDR3 was engineered to include a tyrosine at position Y107, a complete loss of binding to cell surface receptor was observed, which is similar to the ELISA results. This observation points to the role of CDR3 loop in binding to native conformation.

Example 14.3

Activity of 16H7 and 22H5 Variants in Primary Human Adipocytes

FGF21 stimulates glucose uptake and lipolysis in cultured adipocytes and, therefore, adipocytes are often considered to be a physiologically relevant assay. A panel of the engineered variants of 16H7 and 22H5 was shown to exhibit Erk-phosphorylation activity similar to FGF21 in the human adipocyte assay with an estimated EC50 less than 10 nM, as shown in Table 7.

TABLE 7

Activity of Variants in Human Adipocyte Assay			
Core Sequence	SEQ ID NO of Variant Chain	Variant	EC50 (nM)
16H7 Heavy Chain	391	I83T	0.73
16H7 Heavy Chain	393	E16Q + V24F + I83T	0.38
16H7 Heavy Chain	398	D88R + P89A + V90E	0.35
16H7 Heavy Chain	394	E16Q + V24F + I83T + T119L	0.36
		16H7 (WT)	0.53
22H5 Light Chain	403	S94A	1.98
22H5 Light Chain	402	N92Q	3.33
16H7 Heavy Chain	400	Deletion of Y107	1.04
16H7 Heavy Chain	396	I83K	0.39
16H7 Heavy Chain	397	S100I	0.17
16H7 Heavy Chain	401	D109S	0.31
16H7 Heavy Chain	399	D88R + P89A + V90E + S100I	0.14
16H7 Heavy Chain	395	E16Q + V24F + I83T + S100I + T119L	0.24
22H5 Heavy Chain	405	Insertion of Y107	0.51
16H7 Heavy Chain	390	V24F	0.75
16H7 Heavy Chain	392	V24F + I83T	0.37
16H7 Light Chain	386	D49Y	0.60
16H7 Light Chain	387	D49A	0.63
16H7 Light Chain	389	D49A, D91A	1.4

TABLE 7-continued

Activity of Variants in Human Adipocyte Assay			
Core Sequence	SEQ ID NO of Variant Chain	Variant	EC50 (nM)
16H7 Light Chain	388	D91A	1.3
16H7 Light Chain	385	Q16K	0.11
		22H5 (WT)	2.27

Example 14.4

Biacore™ Binding Experiments and Off-Rate Measurement

Binding of 16H7 and 22H5 variants to human β-Klotho was tested using Biacore™ assays. Briefly, mouse anti-His antibody (Qiagen™, Valencia, Calif.) was immobilized on a CM5 chip using amine coupling reagents (General Electronics™, Piscataway, N.J.). His-tagged human recombinantβ-Klotho was captured on the second flow cell to ~100 RU. The first flow cell was used as a background control. 100 nM mAbs were diluted in PBS plus 0.1 mg/ml BSA, 0.005% P20 and injected over the β-Klotho captured on anti-His antibody surface. For kinetic measurement, 0.78~100 nM mAbs diluted in PBS plus 0.1 mg/ml BSA, 0.005% P20 were injected over the β-Klotho surface.

The variants tested are summarized in Table 8:

TABLE 8

Variants Studied in Binding and Off-rate Experiments					
Construct Number	Core Antigen Binding Protein	Heavy Chain Identifier/Variation	Light Chain Identifier/Variation	Heavy Chain SEQ ID NO	Light Chain SEQ ID NO
22H5		H2	L2	31	13
#1, P60881.3	16H7	I83T	L3	391	14
#2, P60880.3	16H7	E16Q + V24F + I83T	L3	393	14
#3, P60890.3	16H7	D88R + P89A + V90E	L3	398	14
#4, P60878.3	16H7	E16Q + V24F + I83T + T119L	L3	394	14
#5, 16H7 WT	16H7	H3	L3	32	14
#6, P60898.3	22H5	H2	S94A	31	403
#7, P60897.3	22H5	H2	N92Q	31	402
#8, P60886.3	16H7	Deletion of Y107	L3	400	14
#9, P60885.3	16H7	I83K	L3	396	14
#10, P60884.3	16H7	S100I	L3	397	14
#11, P60883.3	16H7	D109S	L3	401	14
#12, P60879.3	16H7	D88R + P89A + V90E + S100I	L3	399	14
#13, P60882.3	16H7	Hemibody Heavy Chain	L3	453	14
#14, P60891.3	16H7	E16Q + V24F + I83T + S100I + T119L	L3	395	14
#15, P60889.3	16H7	Insertion of Y107	L3	405	14
#16, P60888.3	16H7	V24F	L3	390	14
#17, P60887.3	16H7	V24F + I83T	L3	392	14
#18, P60894.3	16H7	H3	D49Y	32	386
#19, P60895.3	16H7	H3	D49A	32	387
#20, P60893.3	16H7	H3	D49A + D91A	32	389
#21, P60892.3	16H7	H3	D91A	32	388
#22, P60896.3	16H7	H3	Q16K	32	385
#23, P60899.2	22H5	C109S	L2	404	13

Among the engineered mAbs tested, the majority of them showed tight binding to human β-Klotho, except #15 which showed no binding. Table 9 below shows 100 nM mAbs binding to β-Klotho captured on anti-His. FIG. **33** shows the comparison to off-rate.

TABLE 9

Binding to β-Klotho	
Sample	koff (1/s)
#20, P60893.3	1.9E−04
#11, P60883.3	2.6E−04
#23, P60899.2	3.0E−04
22H5	3.1E−04
#18, P60894.3	3.1E−04
#6, P60898.3	3.5E−04
#13, P60882.3	4.4E−04
#7, P60897.3	5.2E−04
#8, P60886.3	5.3E−04

Example 15

Combinations of Antigen Binding Proteins Show an Additive Effect

Antigen binding proteins representing different binding bins (FIG. **11***a* and *b*) were selected and tested in reporter assays in pairs to determine if the pair of molecules would behave in an additive fashion. Assays were run as follows.

On day one, AM-1/D FGFR1c+β-Klotho Luc clone was seeded in a 96-well plate at 20K cells/well in DMEM+10% FBS medium. The plate was incubated overnight. The following day, the medium was replaced with assay medium (DMEM+0.2% FBS) and incubated overnight. From an antibody working stock (1 mg/mL in PBS), each antibody under study was prepared at a dilution of 2 μg/ml in assay medium. 100 μL of each antibody to be tested was combined in a U-bottom plate. The assay medium was removed from the cells, and 50 μL of the antibody mixtures was transferred to the cells. The antibody mixtures were incubated on the cells for 5 hrs. Lastly, each sample was read-out with SteadyGlo Luciferase reagent (50 μl/well), per the manufacturer's specifications.

Table 10 below is a summary of the activity (% of FGF21 activity from the reporter assay) observed from the study; Table 11 expresses the observed activities with respect to bins.

TABLE 10

Antibody Combination Activity (%)								
			Iso					
			6	5	4	3	2	1
		IgG2k	2G10	16H7	12E4.1	20D4.1	39F7	26H11.1
Iso	IgG2k	ND	−1.1	23.5	25.4	12.5	9.2	17.9
1	26H11.1	17.9	19.1	36.7	21.4	28.3	20.7	
2	39F7	9.2	9.1	37.0	30.8	21.4		
3	20D4.1	12.5	13.5	19.4	32.0			
4	12E4.1	25.4	28.8	41.5				
5	16H7	23.5	27.8					
6	2G10	−1.1						

TABLE 11

Antibody Combinations Expressed in Terms of Bins								
			D	C	B	B	A	A
Bin	Ab ID	Isotype	2G10	39F7	12E4.1	26H11.1	16H7	20D4.1
A	20D4.1	12.5	13.5	21.4	32.0	28.3	19.4	
A	16H7	23.5	27.8	37.0	41.5	36.7		
B	26H11.1	17.9	19.1	20.7	21.4			
B	12E4.1	25.4	28.8	30.8				
C	39F7	9.2	9.1					
D	2G10	−1.1						

Surprisingly, several pairs of molecules showed an additive effect. As shown in FIGS. **34** and **35**, respectively, 39F11 and FGF21 showed an additive effect when measured in the reporter assay of Example 5, as did 16H7 and 39H11.

Summarizing the data from this set of experiments, it was observed that antigen binding proteins from the same binding bin, e.g., 16H7 when paired with 20D4 (both from Group A), the summed activity was not additive. This was also observed when 12E4 was paired with 26H11 (both from Group B). Additionally, paired antigen binding proteins from non-overlapping bins showed additive activities, e.g., 16H7 (Group A) paired with 26H11 or 12E4 (Group B), or paired with 39F7 (Group C). Further, antigen binding proteins 26H11 and 12E4 (Group B) showed additive effect when combined with Abs from Group A but not Group C, suggesting there may be some overlap between the binding sites of Group B and Group C and/or that the activation conformations induced by the antigen binding proteins from Group B and Group C are not mutually compatible. Finally, as expected, when a functional antigen binding protein is paired with a non-functional antigen binding protein (e.g., 2G10) which binds to a distinct and non-overlapping binding site from Group A, B or C, there is no effect upon the activity from the functional antigen binding protein from Group A, B or C.

Collectively, this data suggests that the disclosed antigen binding proteins can be co-administered to enhance the effect that a given antigen binding protein may provide on its own.

Each reference cited herein is incorporated by reference in its entirety for all that it teaches and for all purposes.

The present disclosure is not to be limited in scope by the specific embodiments described herein, which are intended as illustrations of individual aspects of the disclosure, and functionally equivalent methods and components form aspects of the disclosure. Indeed, various modifications of the disclosure, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

SEQUENCE LISTING

The patent contains a lengthy "Sequence Listing" section. A copy of the "Sequence Listing" is available in electronic form from the USPTO web site (http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US09284378B2). An electronic copy of the "Sequence Listing" will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

What is claimed is:

1. An isolated monoclohal antibody that specifically binds to human B-Klotho polypeptide comprising SEQ ID NO: 7, wherein said antibody comprises heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of SEQ ID NO: 122, SEQ ID NO: 133, and SEQ ID NO: 148 and a light chain variable region comprising CDRs comprising the amino acid sequences of SEQ ID NO: 166, SEQ ID NO: 176, SEQ ID NO: 188.

2. The antigen binding protein of claim **1**, wherein the antigen binding protein is a human antibody, a humanized antibody, chimeric antibody, a monoclonal antibody, a polyclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an $F(fab')_2$ fragment, a domain antibody, an IgD antibody, an IgE antibody, an IgM antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, an IgG4 antibody, or an IgG4 antibody having at least one mutation in the hinge region.

3. A pharmaceutical composition comprising the isolated monoclonal antibody of claim **1** and a pharmaceutically acceptable carrier.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,284,378 B2
APPLICATION NO. : 12/960407
DATED : March 15, 2016
INVENTOR(S) : Shaw-Fen Sylvia Hu et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Claim 1
Cancel the text beginning with “1. An isolated monoclohal antibody” at Column 201, Line 36 to and ending “SEQ ID NO: 188.” in Column 201, Line 44, and insert the following claim:

--1. An isolated monoclonal antibody or antigen binding protein that specifically binds to human beta-Klotho polypeptide comprising SEQ ID NO: 7, wherein said antibody comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of SEQ ID NO: 122, SEQ ID NO: 133, and SEQ ID NO: 148 and a light chain variable region comprising CDRs comprising the amino acid sequences of SEQ ID NO: 166, SEQ ID NO: 176, SEQ ID NO: 188.--

In Claim 2
Cancel the text beginning with “antibody” at Column 202, Line 35 to and ending “hinge region.” in Column 202, Line 42, and insert the following:

--antibody, chimeric antibody, a polyclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an F(fab')2 fragment, a domain antibody, an IgD antibody, an IgE antibody, an IgM antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, an IgG4 antibody, or an IgG4 antibody having at least one mutation in the hinge region.--

Signed and Sealed this
Twenty-eighth Day of February, 2017

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office